Memory deficits in epilepsy patients referred to tertiary epilepsy centres

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Voor mijn ouders

Voor Jolanda, Nyls en Ynès

..omdat onvergetelijkheid bestaat..

CHAPTER 1

Aims of the Study

INTRODUCTION

Epilepsy first was described by Hippocrates approximately 400 b.c. as a state in which somebody was "seized by forces from without" (McIntosh, 1992). In the second half of the 19th century, Hughlings Jackson gave a more modern definition and stated that epilepsy was "an occasional, sudden, excessive, rapid and local discharge of grey matter" (Haynes & Bennet, 1992). Jackson also proposed a system of classification for these different forms of seizures and epileptic disorders. With the introduction of the electroencephalogram (EEG) the clinical manifestations could be linked to the origin and topographical location of the abnormal discharges underlying the seizures. This has led to an operational definition of epilepsy as *'the occurrence of transient paroxysms of excessive or uncontrolled discharges of neurons, which may be caused by different aetiologies and lead recurrently to epileptic seizures'*. Epileptic seizures are considered as intermittent, paroxysmal, stereotyped disturbances of consciousness, behaviour, emotion, motor function, perception or sensation, that may occur singly or in combination (Appleton & Gibbs, 1998).

CLASSIFICATION OF EPILEPTIC SEIZURES AND EPILEPTIC SYNDROMES

There have been many attempts to classify epileptic seizures and epileptic syndromes. The most commonly used classification of epileptic seizures is the International Seizure Classification of the International League against Epilepsy (ILAE), which is based on the clinical manifestations of the seizures (ILAE, 1981). In this classification seizures are divided in partial, generalized and unclassified seizures.

In addition to seizure classification, a number of distinctive epileptic syndromes have been described (ILAE, 1989). Epilepsy syndromes are classified in four groups: location-related, generalized, undetermined and special syndromes. Within these groups the epilepsy syndromes are further divided in idiopathic, cryptogenic, and symptomatic. While in idiopathic epilepsies the syndromes are presumed to be inherited, symptomatic epilepsies are

based on identifiable structural brain diseases. In cryptogenic epilepsies a symptomatic epilepsy is suggested but the causation remains unknown (Dreifuss & Henriksen, 1992).

INCIDENCE AND PREVALENCE OF EPILEPSY

Epilepsy is the most common neurological condition. In a recent study in the Netherlands the incidence has been estimated to be 0,72 / 1000 person-years (Shackleton, Westendorp, Kasteleijn-Nolst Trenité, De Boer, Herings, 1997). The cumulative incidence is estimated between 2 and 5%. The incidence is relatively high in the first 20 years of life, drops in the next two decades, and increases slightly in later life (Sander & Shorvon, 1996).
In the Western countries the prevalence of active epilepsy has been estimated to be between 4 and 10 per 1000. Shackleton et al. (1997) showed the prevalence of active epilepsy in the Netherlands to be 4,8 per 1000 inhabitants. Although there is some debate about the definition of active epilepsy, most researchers consider epilepsy to be active if patients have had seizures within the last 2 years (Sander & Shorvon, 1996). About 70% of all patients with epilepsy will become seizure-free in the first two years after the first seizure. Epidemiological data indicate that as a group, these patients are neuropsychologically and socially most well adjusted (Trostle, Hauser, Sharbrough, 1989). Nevertheless 20% of the patients that are seizure-free experience negative consequences of having epilepsy, in employability, social-economic status, or social relations (Specht, 2001).The remaining 20-30% patients will develop an active or even a refractory epilepsy. Patients with refractory epilepsy continue to have seizures despite optimal treatment with antiepileptic drugs, and they find seizures or the daily consequences of their epilepsy disabling (Hart & Chaplin, 2001). These consequences might include behavioural problems and disorders of general intellectual functioning or specific cognitive dysfunction, such as memory deficits. Within the area of cognitive epilepsy related impairments, memory problems are the most frequently reported by patients (Hendriks, Renier, Eling, 2004). Hart and Chaplin (2001) suggest that within a framework of comprehensive care not only neurological treatment but also psychological support should be offered.

In the Netherlands comprehensive care for patients with refractory seizures is offered by three specialized tertiary epilepsy centres, i.e., Epilepsy Centre Kempenhaeghe in Heeze, Epilepsy Centre Hans Berger Clinic in Breda, and Stichting Epilepsie Instellingen Nederland

in Heemstede. In this clinical study patients are included from these specialised tertiary epilepsy centres.

DIAGNOSIS AND TREATMENT OF EPILEPSY

The diagnosis of epilepsy is primarily based on the clinical features of the seizures that may be supported by an electroencephalogram (EEG). Structural neuroimaging (Computed Tomography -CT, Magnetic Resonance Imaging –MRI), may provide indications for the presence and localisation of structural brain damage underlying the seizures and confirm the diagnosis of a symptomatic or cryptogenic form of epilepsy. Furthermore, functional imaging techniques, such as single-photon emission tomography (SPECT), positron emission tomography (PET), and functional MRI (fMRI), enable researchers and clinicians to map cerebral activation and directly describe brain correlates of specific behaviours. In addition neuropsychological assessment is used for determining the functional deficits of patients and to confirm subjective problems experienced and is considered as a standardized aspect in the care of the specialised epilepsy centres in the Netherlands.

The main treatment of epilepsy is the prescription of antiepileptic medication. Antiepileptic drugs produce changes in the excitation levels of the brain and may affect cognitive functions. Cognitive or behavioural side effects are usually fairly modest in monotherapy, while patients treated with polytherapy are at increased risk of cognitive impairments (Ortinski & Meador, 2003). For those patients who develop pharmacologically intractable seizures, epilepsy surgery can be considered.

AIMS OF THIS STUDY

During the period 1998-2001, patients with epilepsy were consecutively included from the three epilepsy centres in the Netherlands (Epilepsy centre Kempenhaeghe, Heeze; Epilepsy Centre Dr. Hans Berger Clinic, Breda; Epilepsy Institute of the Netherlands, SEIN, Heemstede) in a prospective study.

Patients were considered for inclusion in this study if they met the following criteria:

1. Subjective memory complaints considered relevant for a neuropsychological assessment by the treating neurologist;

2. Aged between 16 and 60 years, to avoid the effects of normal aging on memory;
3. Without global intellectual disability, to avoid interfering effects of subnormal intelligence on memory performance;
4. No signs of clinical depression or aphasia, because of their interference with memory functions;
5. No signs for a progressive neuropathological condition, such as cerebral tumours, or dementia;
6. No history of status epilepticus;
7. No seizures within 24 hours before neuropsychological assessment, to avoid postictal influence on memory functions.

These patients were invited for a neuropsychological assessment. Within this context all patients completed a memory questionnaire to evaluate the type and severity of memory problems that occur in everyday life, and neuropsychological tests to examine memory functions. Because memory functions cannot be assessed in isolation from related cognitive functions, general intellectual abilities, language functions, visual spatial functions, concentration and attention, executive functions, and personality factors, were also included in the test battery.

The results of this study are presented in the following chapters:

Chapter 2 presents a review of the literature on memory impairment in epilepsy, the neuropsychology of memory and the neuropsychological assessment of memory complaints in patients with epilepsy.

Chapter 3 is focused on the type of memory complaints patients with epilepsy complain about in daily life. Furthermore, the relationship between subjective memory complaints and several epilepsy-related factors, such as seizure type, lateralisation and location of the focus, etiology, duration, age at onset and antiepileptic medication, is evaluated.

In *Chapter 4* a description of the different memory profiles is presented. These memory profiles are based on a neuropsychological test battery using the accepted memory subsystems, i.e. verbal short term memory, verbal long term memory, non verbal short term memory, and non verbal long term memory.

Chapter 5 aims to explore the dominant risk factors for memory impairment in patients with epilepsy. The effects are evaluated of the aforementioned epilepsy-related

factors on memory impairment, and whether these factors are related to the same aspects of memory subsystems as presented in chapter 4.

Chapter 6 addresses with the question whether short term recognition memory deficits are found in patients with mesial temporal sclerosis (MTS). In addition, it is hypothesized that patients with a left MTS will show deficits on a task for verbal recognition and in tasks that presents the information serially. For patients with a right MTS impairments are expected on a task for non verbal recognition and simultaneously presented material.

In *Chapter 7* the differential involvement is studied of the right and left mesial temporal lobe in various forms of spatial memory: spatial search, positional memory versus object-location binding, and coordinate versus categorical processing.

Finally, a summary and the main conclusions are provided in *Chapter 8*.

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CHAPTER 2

Neuropsychological Assessment of Memory Functions in Patients with Refractory Epileptic Seizures: Review of the Literature

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INTRODUCTION

The association between cognitive impairments and epilepsy already has been described in the 17th century (Bennet, 1992). According to this author, Thomas Willis stated in his Oxford Lectures that: "It often happens that epileptic patients, during their paroxysm and afterwards, suffer a severe loss of memory, intellect, and phantasy..". However, this clinical impression was based on the ictal and postictal effect of seizures. As early as 1885, Gowers was probably the first who suggested that memory deficits are one of the most frequent interictal cognitive dysfunctions in patients with epilepsy (Gowers, 1885).

Nevertheless, only during the last two decades has special attention been paid to memory problems. In the past, most investigations were oriented at the global intellectual capacities. A significant limitation these early studies were that they were typically based on institutionalized patients, which has biased the conclusions by sampling error. Secondly, although the development of IQ tests as an objective index of intellectual ability has been a major progress in psychology, they are not particularly sensitive in measuring cognitive deficits in people with brain injuries (Lezak, 1995). Another problem in these studies is that disease and seizure related factors known to affect cognitive functioning in patients with epilepsy were not controlled.

The development in neuropsychology of a process oriented approach in evaluating specific cognitive abilities in epileptic patients led to more comprehensive assessment procedures (Reitan, 1974; Dodrill, 1978, 1981). Except the modified version of Dodrill's test battery in 1981, these early assessment batteries were less focused on memory testing. The developments in neurosurgical treatment and especially the risk for post surgical amnesia of patients undergoing unilateral temporal lobectomy have led to an increasing emphasis on the neuropsychological assessment of memory functions of patients with epilepsy (Jones-Gotman, Smith, Zatorre, 1993).

However, in the last three decades conclusions about cognitive function in people with epilepsy are determined by investigations on neurosurgical candidates, and this specific subpopulation of mainly patients with temporal lobe epilepsy also is not representative of

patients with epilepsy in general. Knowledge in neuropsychology has probably gained more from pre-/postoperative studies on patients with epilepsy who have undergone surgery than otherwise.

MEMORY COMPLAINTS IN EPILEPSY

Methodological issues

Memory dysfunction is the most frequently reported cognitive complaint in the general population and in patients with epilepsy. Aldenkamp, Hendriks, Vermeulen (1999) estimate that 15% to 20% of patients with refractory epilepsy suffer from memory impairment. Although, in clinical practice subjective memory complaints always have to be taken seriously and are considered as a basic assumption in memory rehabilitation for patients with epilepsy, additional information is necessary to verify complaints in daily life (Helmstaedter, 2001; Hendriks, 2001). Unfortunately, memory complaints do not necessarily involve memory deficits. In fact, only moderate correlations (i.e. 0.30-0.40) are found between self-reported memory complaints and objective neuropsychological test results (Berg, 1993; Brown, Dodrill, Clark, & Zych, 1991; O'Shea, Saling, Bladin, & Berkovic, 1996). Helmstaedter, Hauff, & Elger (1998) showed that subjective memory complaints and objective memory measurements, only correlated well when testing did not indicate memory deficits. Several reasons have been suggested for this lack of correlation.

First, neuropsychological test results are evaluated in laboratory settings and as a consequence may not reflect real life behaviour. In psychometrical terms it means that the ecological validity of neuropsychological tests may not be sufficient. Elixhauser, Leidy, Meador, Means, & William (1999) used the Rivermead Behavioural Memory Test (RBMT), which is presumed to be a psychometrically based test for everyday memory performance, and even these performances showed marginal correlations with subjective indications of cognitive functioning.

Second, it is suggested that this discrepancy reflects the fact that memory problems are easy to recognise in daily living. Thus other cognitive dysfunctions such as attentional deficits or language disorders may go unnoticed, whereas the consequences may be experienced subjectively as memory impairment. In a study of O'Shea et al. (1996) patients with temporal lobe epilepsy were compared to patients with idiopathic epilepsies, and they found that the

performances on a word association task correlated positively with a memory questionnaire. A frequently reported memory complaint in the general population and in patients with epilepsy is the 'tip of the tongue' phenomenon (Thompson & Corcoran, 1992). It is still unclear whether such difficulties in word-finding are the result of language or memory dysfunction. Consequently, patients may overestimate their memory impairment in daily life.

Finally, subjective memory functioning is strongly related to personality factors and mood. Of course it is well known that the emotional context in which information is encoded influences memory functioning. This may also be related to the clinical observation that some patients with epilepsy complain about forgetting emotionally loaded episodes more easily. Case number 4 in the prologue is a good example of this relationship. Vermeulen, Aldenkamp and Alpherts (1993) found that patients with epilepsy have more memory complaints than actual deficits on memory tests and suggest that this may be related to personality factors, especially neuroticism. Also, Giovagnoli, Mascheroni and Avanzini (1997) report that memory complaints were most explained by the extent of anxiety and depression patients indicated. Also, Deutsch, Saykin and Sperling (1996) suggested that depression plays an important role in so-called metamemory in patients with temporal lobe epilepsy. They reported more depression than controls, but there were no differences in the level of depression or the accuracy of metamemory between patients with right or left temporal lobe epilepsy. If patients indicated to be more depressed then they underestimated their memory, but their actual memory performances with neuropsychological testing did not differ.
At the level of the individual patient this implies that in clinical practice it is almost impossible to give a good judgement of a patient's memory complaints. Research is mostly based on group comparisons, whereas clinical decisions have to be made on individual test data and on what the patient reports. In addition these groups are rather small, mostly consisting of patients with temporal lobe epilepsy for presurgical evaluation and less well controlled for other epilepsy related factors.

NEUROPSYCHOLOGY OF MEMORY

Cognitive models of memory functions

The concepts of learning and memory are closely related. Squire (1987) defines learning as the process by which new information is acquired, while memory refers to the persistence of

learning. The term memory is usually used to refer to a unitary, passive unit. However, experimental research in cognitive psychology and neuropsychological studies of patients with brain damage has shown that memory is the collection of a number of active cooperating functional subsystems. Three distinctional stages of memory are hypothesised: encoding, storage, and retrieval (Gazzaniga, Ivry, & Mangun, 1998). Encoding is separated by the acquisition and consolidation of information, while storage is the result of these processes by which a permanent record is created. With retrieval stored information is recollected in consciousness if necessary. These subsystems are differentiated by:

1. The length of time for which information is stored.
2. Their storage capacity.
3. The type of information that is stored.

The most influential 'time-based' structure of memory was that proposed by Atkinson and Shiffrin (1968). They described a modal model of memory as consisting of three sequential stages: sensory register, short-term and long-term storage. However, clinical observations showed that patients with a deficient short-term memory can learn and consolidate information, which is not congruent with a serial model of memory. The indication that these processes act in parallel, leading originally Baddeley and Hitch (1974) to hypothesize that short-term memory is not a unitary store but a multi-component working memory with a limited capacity, for performing mental operations. They propose that working memory consists of at least three subsystems: a phonological loop and a visuo-spatial scratchpad, for coding acoustically and visuo-spatial information respectively, and a central executive that acts as a controlling interface between the two subordinate systems. Another characteristic of short-term storage in working memory systems is that their capacity is limited. Information can be lost by decay, or especially by interference of other sensory inputs (Baddeley, 1995a).

When information is not operated actively and stored for a significant time we refer to long-term memory. Like short-term memory, the structure of long-term memory consists of many cooperating subsystems. The concept of a distinction between explicit and implicit memory proposed by Tulving (1972), is consistent with the description of a declarative and non-declarative memory by Squire and Zola-Morgan (1988, 1992).

Non-declarative memory refers to knowledge for what there is no conscious access to, such as all kinds of motor skills and tasks that do not require intentional recollection. Non-declarative memory is preserved in patients with the amnesic syndrome. Declarative memory contains semantic an episodic knowledge. In semantic memory our knowledge of the world is collected. It refers to the meaning of words and other facts that we gradually learn in school, and we remember in the absences of the context in which it was learned. With episodic memory we store and recollect personal events and experiences and it is this system that is very vulnerable to brain damage. The functional structure of the long-term storage systems is highly organized and is based on forming associations between two or more bits of information. It is assumed that by the association of information our knowledge accumulates, and in this respect the total capacity of the long-term memory system seems to be unlimited (Baddeley, 1995b).

As described in the next paragraph, the most frequently used distinction in type of information is between verbal and non-verbal information.

Memory functions and the brain

Because much of the cognitive conceptualisations of memory are derived from knowledge of distinctive memory deficits in patients with brain damage, it has become clear that the entire brain is involved in most memory processing. Nevertheless, it is apparent that some cerebral structures have a more important role than others. Squire (1987) concluded that memory is distributed in a localizable and non-localizable way. He states that memory cannot be assigned to one specific brain location. The total amount of information stored in many cooperating cerebral areas that are functionally similar.

Clinical neuropsychological research has provided much of our current knowledge about the neural basis of human memory (Tranel & Damasio, 1995). Prolonged alcohol abuse may lead to thiamine deficiencies and result in damage of the diencephalic structures, especially the dorsomedial nucleus of the thalamus and the mamillary bodies, and causes severe memory deficits as part of the Korsakoff syndrome. The most well-known and intensively studied patient in neuropsychology is H.M., who received a bilateral resection of the mesial temporal lobes to control his epileptic seizures. The extraordinary aspect of H.M.'s amnesia is that it is very profound, pervasive, and selective, affecting only certain facets of his memory and preserving others, like for instance non-declarative memory. Other patient

studies have shown that a restricted lesion to the CA1 field of the hippocampus could cause an anterograde amnesia that was almost as profound as that of H.M. (Rempel-Clower, Zola, Squire, & Amaral, 1996). Since these initial studies, the involvement of the temporal cortex and the mesial temporal structures (e.g. the hippocampal complex) has been proven, even though this involvement sometimes may be overestimated. The hippocampal complex plays a crucial role in the acquisition and consolidation of new episodic knowledge, and is not essential for short-term or working memory processes. Damage to the hippocampal formation disrupts the interaction with the neocortex and consequently the forming of long-term memories, which result in anterograde memory deficits. When the hippocampal complex in the left hemisphere is damaged it mostly reduces learning of verbal information. Damage of the right hippocampal formation causes specific problems in acquiring non-verbal knowledge. Damage of the lateral temporal cortex affects the retrieval of previously learned information, which results in retrograde amnesia. Analogous to the functional lateralization of the mesial temporal structures, the temporal cortex of the left hemisphere is specialized in the retention of verbal semantic information and the right temporal cortex is involved in non-verbal knowledge such as the storage of faces.

Frontal brain structures also play an important role in memory. There is some debate about whether the frontal lobes have an additional function or participate directly in memory. Lesions to the frontal cortex produce impairment in the strategic capacities that may result in deficits of prospective memory (i.e. remembering to do something) (Manich, 1997). As a consequence, patients have problems with tasks requiring memory temporal order: they know what, but not in what order (Shimamura, Janowsky, & Squire, 1991). Also, so-called source memory is affected (Janowsky, Shimamura, & Squire, 1989). The recall of the source of information is disrupted because contextual aspects are not associated with the actual information. Finally, the basal forebrain associates different aspects of the material that has to be remembered. The functioning of this cerebral region combines the name, the face and all other different aspects in the memory of a particular person (Tranel, & Damasio, 1995).

MEMORY PROBLEMS AND EPILEPSY: IS THERE A RELATION?

The literature shows a number of epilepsy-related factors that may influence cognitive processes in general and memory functions in particular, in patients with epilepsy:

1. The presence and the localization of lesions.
2. The type of epilepsy and the electroclinical localization of the epileptic focus.
3. The age at onset of the epileptic seizures and the duration of active epilepsy.
4. Seizure frequency.
5. The cognitive side effects of antiepileptic medication.

Presence and the localization of lesions

Epilepsy may be the symptom of many different types of brain pathology, such as brain trauma, brain infections, brain tumours or haemorrhages. All these pathological processes may, by themselves, cause memory deficits without the presence of epileptic seizures. In fact, they are assumed to be the most potent factor for the presence of memory problems. As early as the 1960s it was known that the cognitive abilities of people with symptomatic epilepsy were often less than those with idiopathic epilepsies. In a study of Tarter (1972) the intelligence quotients of patients with symptomatic epilepsies were 4 to 11 points lower, compared to those with idiopathic epilepsies. This relationship had already been described in the studies of Kløve and Matthews (1966). Also, they demonstrated more specific neuropsychological impairment by using the Halstead battery. However, Deutsch (1953) showed similar impairments for epilepsy patients with overt brain damage on learning and memory tests.

The differentiation between symptomatic and idiopathic epilepsy is not as clear as it seems, in this respect. With symptomatic epilepsy there is a definite lesion. With idiopathic epilepsy the lesion is, in fact, unknown. The development of neuroimaging techniques such as MRI and especially functional MRI will increase the number of patients diagnosed as having symptomatic or cryptogenic epilepsies. For instance, many patients who now are diagnosed with the syndrome of mesial temporal sclerosis used to be considered to have a functional lesion. Nevertheless, the general conclusion that patients with symptomatic or cryptogenic epilepsies have more memory impairments as compared to patients with idiopathic epilepsies remained (Brittain, 1980; Lesser, Luders, Wyllie, Dinner, & Morris, 1986).

It is still not determined whether sclerosis of the hippocampus is a cause or consequence of epileptic activity. Bertram, Lotham, & Lenn (1990) investigated these two models in an animal study. The results showed that hippocampal damage may be rather acute

an the expected accumulating effect of seizures was in fact quite small. It was concluded that the hypothesis of progressive neuron loss in the hippocampus as an accumulated result of recurrent seizures could not be supported. In the early human studies of Dam (1980, 1982) he concluded that neuron loss is related to the frequency of tonic-clonic seizures and the duration of the active epilepsy (more than 30 years). Neuron loss was not related to a certain type of epilepsy and in his opinion it must be regarded as an cumulating an continuous process. Additionally, brain damage preceding the onset of epileptic seizures can also be an influence. In a study of McMillan, Powell, Janota, & Polkey (1987) it was suggested that hippocampal sclerosis can be the cause as well as a consequence of epileptic activity.

Unilateral damage of the hippocampal structures results in material-specific memory deficits. Some studies have examined the relationship between hippocampal sclerosis and memory function. In a quantitative MRI-study Lencz, McCarthy, Bronen, Scott, Inserni, Sass, Novelly, Kim, & Spencer (1992) showed a significant relationship between a low hippocampal neural density the left temporal lobe and the immediate and delayed recall of the subtest Logical Memory from the Wechsler Memory Scale-revised (WMS-r). Sass, Sass, Westervelt, Lencz, Novelly, Kim, & Spencer (1992) investigated the correlation between neuron loss in specific areas of the hippocampus and different verbal functions. No correlation was found between verbal intelligence, other language functions and immediate and delayed story recall. However, significant correlations were described between the percentage of retention of logical coherent verbal information and neuronal loss in the hippocampal areas CA3 and CA4, for patients with a left temporal focus. In a later study they used a verbal learning task because these tasks are better in distinguishing between patients with left or right hippocampal sclerosis (Sass, Westerveld, & Buchanan, 1994). The left temporal lobe group was more impaired in verbal learning than those with right temporal hippocampal sclerosis. Again, the correlation was found in those with neuron loss in the areas CA3 and CA4.

Nevertheless, these rather straightforward results Giovagnoli, Casazza and Avanzinni (1996) have not found differences in verbal learning in patients with symptomatic epilepsies caused by hippocampal sclerosis or glioma, and patients with cryptogenic temporal lobe epilepsy. Recently, Giovagnoli and Avanzinni (1999) found that patients with temporal lobe epilepsies have some learning and memory impairments irrespective of the presence and type of a lesion, and conclude that the epileptic discharges themselves cause memory deficits

more. Also, Vargha-Khadem, Isaacs, Van der Werf, Rob & Wilson (1992) found that in children with hemiplegic cerebral palsy the structural damage has no major effects on learning and memory, compared to other epilepsy related factors such as age at seizure onset.

In general, the relationship between right hippocampal neuron loss and non-verbal memory deficits seems less strong. To our knowledge only in two recent studies significant correlations were described between a lowered right hippocampal volume and test performances on tests for spatial memory (Matkovic, Oxbury, Hiorns, Morris, & Carpenter, 1995; Abrahams, Morris, Polkey, Jarosz, Cox, Graves, & Pickering, 1999). Some authors suggest that the lack of significant results in patients with right temporal lobe lesions is related to the psychometric difficulties to develop tasks for non-verbal memory (Moore & Baker, 1997). For this Jones-Gotman (1996) used self-developed verbal and non-verbal learning tasks in patients with left or right hippocampal sclerosis. The advantage of her technique is that it follows the same procedure in both tests and she found the expected dissociations between left and right patients groups.

Type of epilepsy and the electroclinical localization of the epileptic focus

An epileptic focus in the absence of an established cerebral lesion may indicate a functional impairment rather than a lesion and deactivate local cerebral systems that are of importance for memory functioning. Most of the research on this factor is based on patients who are candidates fro surgery for their pharmacologically intractable epilepsy. The well-described localization of the electroclinical epileptic activity in these patients makes it possible to study correlations between local dysfunctions in the brain and the pattern of neuropsychological deficits. However, this is a selected group within the total population of patients with refractory epilepsy, and there is a risk of sample selection bias. Another problem with pre-/postoperative studies may be that cognitive function is influenced more by the cortical resection itself than by the epileptic focus.

An epileptic seizure or epileptic discharges can disrupt all kinds of functions, including memory. Epileptic activity in the hippocampal formation can disrupt the process of long-term potentiation *in vitro* (Moore, Barr, & Wilson, 1993). Long-term potentiation is crucial for neuronal plasticity that is responsible for the storage of episodic information. The process of long-term potentiation can last a few minutes to several days, so an epileptic seizure or discharge may influence memory more than just during the actual episode with

discharges. Halgren, Stapleton, Domalshi, Swartz, Delgado-Escueta, Walsh, Mandelhern, Blahd, & Ropchan (1991) found that the performance of patients with an episode of partial seizures was much more impaired on memory tests two days afterwards than two weeks later. Of course, this does not mean that a disturbance in long-term potentiation is the cause of these deficits, but it illustrates that it is not just the epileptic seizure that is of importance.

Some studies found evidence for transient memory deficits as a consequence of subclinical activity in the temporal brain structures during the execution of working memory tasks (Aarts, Binnie, Smit, &Wilkins, 1985). Left-sided discharges caused deficits in verbal learning, and discharges in the right hemisphere resulted in deficits of non-verbal learning. Support for a direct relation between epileptic activity and memory deficits can be found in case studies that describe subjects with so-called amnesic epileptic attacks, transient memory deficits being the only clinical symptom (Pritchard, Holmstrom, Roitzsch, & Giacinto, 1985; Gallasi, Morreale, Lorusso, Pazzaglia, & Lugaressi, 1988). Electro-encephalogram registrations show discharges from the hippocampus and medial temporal brain areas, without exception. When antiepileptic drugs are used, the amnesic attacks disappear in most cases. The methodological problem with these case reports is that these studies are done retrospectively and are based on subjective complaints. Brigman, Malamut, Sperling, Saykin, & O'Connor (1989) tested two patients during subclinical hippocampal seizures and concluded that these seizures were responsible for the memory deficits.

Also, in clinical studies with patients with functional abnormalities on the EEG it is well documented that patients with epileptic seizures located in the temporal lobes have more memory impairments than patients whose seizures originate from extratemporal lobe regions of the brain Furthermore, unilateral epileptic abnormalities of the temporal and especially the mesial temporal structures results in material-specific memory deficits. Verbal learning and memory impairments are associated with an electro-clinical localization in the left temporal lobe regions (Hermann, Wyler, Richey & Rea, 1987; Ribler & Rausch, 1990; Giovagnoli & Avanzinni, 1999; Blake, Wroe, Breen & McCarthy, 2000; Kwan & Brodie, 2001). Although less strong, some studies suppose an association between right temporal lobe abnormalities and nonverbal memory difficulties (Helmstaedter, Pohl, Hulfnagel & Elger, 1991; Baxendale, Thompson & Van Paesschen, 1998; Loring, Hermann, Lee, Drane & Meador, 2000). Bergin, Thompson, Baxendale, Fish, & Shorvon (2000) studied remote memory for public events and

found that patients with bilateral temporal abnormalities performed most worse, whereas patients with unilateral temporal abnormalities did not show significant differences.

When seizure type is analyzed, more cognitive impairment is found in patients with tonic-clonic generalized seizures when compared with partial seizures (Dodrill, 1992a; Perrien, Gershengorn, & Brown, 1991). However, studies that reported these findings rarely use adequate examination of memory functions. Already in the mid-fifties, Quadfasel and Pruyser (1955) found that memory was specifically impaired in a group with partial seizures a suggesting that is confirmed by other authors (Milberg, Greiffenstein, Lewis, & Rourke, 1980). In several recent studies the specific memory problems in patients with complex partial seizures have been confirmed, and these investigations have consistently documented material-specific memory deficits equally to those found with cerebral lesions (Hermann, Wyler, Richey & Rea, 1987; Bornstein, Drake & Pakalnis, 1988). However, this finding cannot be interpreted in isolation because most of these patients will have temporal lobe dysfunctions. In contrast, some studies have not shown a clear relationship between seizure type and memory impairment (Scott, Moffet, Matthews, & Ettlinger, 1976; Loiseau, Strube, Broustet, Battelochi, Bomeni, & Morselli, 1983).

Age at onset of epileptic seizures and the duration of active epilepsy

In general, studies of intellectual and specific cognitive functions in people with epilepsy indicate that an early age at onset of seizures in life and a consequently long duration of a seizure disorder is associated with a higher risk for cognitive dysfunction (Bennet, 1992; Aldenkamp, Alpherts, Dekker & Overweg, 1990; Saykin, Gur, Sussman, O'Connor, & Gur, 1989).

Matthews and Kløve (1967) found that in patients with tonic-clonic seizures of early onset, intellectual functioning was more impaired. Also, Dikmen, Matthews and Harley (1975, 1977) described lower intelligence scores for adult patients with a seizure onset of tonic-clonic seizures before 5 years of age, compared with a group of patients in whom seizures started between the age of 10 and 15 years. It is hypothesized that cerebral dysfunction before the age of 5 years may influence lateralization patterns of cognitive function. In more than 96 per cent of the right-handed population and 67 per cent of the left-handed population, the left hemisphere predominantly mediates language functions and the right hemisphere mediates visual spatial abilities. This developmental lateralization process

can be disrupted by a left-sided epileptic focus before the age of 5 years. Children may develop pathological left-handedness and the mediation of language functions may consequently shift from the left to the right hemisphere. As a consequence, visual spatial abilities may not develop to their full potential; the so-called 'crowding-effect' (Spreen, Tupper, Risser, Tuokko, & Edgell, 1984). Van der Vlugt and Bakker (1980) found support for this hypothesis in a study with adult patients with epilepsy. Giovagnoli and Avanzini (1999) suggest that this particularly accounts for semantic memory, because facts and other semantic abilities are acquired early in life. In fact, Devinsky, Perrine, Llinas, Luciano, & Dogali (1993) found that an early age at onset of seizures in the left temporal lobe results in a more diffuse and atypical localization of language functions. In a study with patients with early onset seizures originating in the left mesial temporal structures as a consequence of hippocampal scleroses Seidenberg, Hermann, Shoenfeld, Davies, Wyler, & Dohan (1997) found that these abnormalities caused a reorganization of verbal memory functions. In a recent multicentre study with a large population of epilepsy patients age at onset was found to be the best single predictor of intelligence and the General Memory index of the Wechsler Memory Scale-Revised, although the effect was marginal (Strauss, Loring, Chelune, Hunter, Hermann, Perrine, Westerveld, Trennery, & Bar, 1995). The results showed that the combined influence of the epilepsy variables and other patient characteristics was only modest. Nevertheless, as may be expected, Dodrill (1992b) suggests that age at onset may be more strongly related to cognitive function than to other seizure-related variables. An early onset of seizures increases the risk of brain damage, developmental problems, lesser education, and the early prescription of medication with negative side effects on cognitive functioning and the possibility of an accumulating effect of seizure frequency on cerebral organization. Thompson (1991) assumes that especially an early age at onset and a longer duration of active epilepsy is related to memory deficits.

The unique contribution of duration epilepsy also is an influential variable with respect to poorer intellectual ability and cognitive decline (Singhi, Bansal, & Singhi, 1992; Delaney, Rosen, Mattson, & Novelly, 1980; Rodin, Schmaltz, Twitty, 1986). In the study of Delaney et al. (1980) they investigated also memory functions of patients with localization related epilepsies were investigated, and they concluded that those with a longer duration showed more deficits. In the study of Strauss et al. (1995) no consistent relation between duration of seizure and cognitive functioning was found. Also, Dodrill and Matthews (1992) found only a

marginal correlation between full scale IQ and duration of disorder and conclude that this factor compared to others 'tends to be somewhat weaker than others'. One reason why duration has little direct impact on cognitive functioning might be that many patients in research groups have years without seizures. Farwell, Dodrill, and Batzel (1985) cocluded that there was a stronger causal relation between cognitive function and the number of years in which seizures actually occurred. Hermann and Whitman (1986) agree with these authors and suggest in future research that duration be defined as the number of years in which the epilepsy was active.

Seizure frequency

One might argue that if seizures cause cognitive deficits then more seizures will cause more sever cognitive deficits (Bennet, 1992; Kwan & Brodie, 2001). The literature, however, does not always support this relationship, possibly because of the plethora of methodological problems related to this factor (Thompson, 1991).

First, seizure frequency at one particular moment in time is often the only parameter available, and not the total amount of seizures in the patient's life. Yet this latter factor may be more important for explaining cognitive impairment. If the total amount of seizures is taken into account, it is always estimated. Second, seizure severity may be important, but a clear estimation of severity is not always available. Third, a high seizure frequency may simply reflect the severity of the underlying cerebral pathology.

Nevertheless, already in the study of Blackemore, Fettinger, and Falconer (1966) it was indicated that a high seizure frequency affected verbal intelligence more than did the severity of pathologic changes. Also, more recent data do suggest that the effect of seizure frequency is important. Loiseau et al. (1983) for example, did not find memory impairment in patients with seizure remission or in patients with low seizure frequency, and Dodrill (1986) found positive evidence for cognitive impairment in patients with high seizure frequency. In particular, patients who had more than 100 tonic-clonic seizures in their lives showed most impairments. Interestingly, patients who experienced one or more episodes of status epilepticus in their lives showed even more cognitive impairment. It therefore seems important to consider status epilepticus as a separate seizure-related factor when studying cognitive deficits.

Cognitive side effects of antiepileptic medication

The relationship between memory deficits and epilepsy was described long before the introduction of current antiepileptic drugs. However, since the development of a variety of antiepileptics it has been indicated that some of these drugs may cause cognitive side effects, including memory problems. In particular, high serum levels or toxic doses will impair cognitive functioning (Trimble, 1987). In clinical practice most concern should be given to possible cognitive deficits caused by antiepileptic medication within the therapeutic range. Another more general finding is that the negative effects of polytherapy are more profound than of monotherapy (Trimble, 1987; Kwan & Brodie, 2001). In a recent review Kwan and Brodie (2001) conclude that a reduction of antiepileptic medication or an alteration from polytherapy to monotherapy may improve cognition. In a study with medically intractable epilepsy patients with seizures originating in the left temporal lobes by whom the antiepileptic medication was reduced, Durwen and Elger (1992) found significant improvements in verbal memory performances.

Recent reviews and meta-analyses have found most evidence of drug-induced cognitive impairments for phenobarbitone and phenytoin, and information processing speed and memory are found to be the critical areas (Vermeulen & Aldenkamp, 1995; Aldenkamp, 2001). Aldenkamp (2001) concludes that the use of valproate may result in mental slowing, while for carbamazepine minimal adverse cognitive effects are reported. Studies of the cognitive side effects of most recently developed antiepileptic drugs are still insufficient to give an adequate answer.

Implications for clinical practice

Memory must be considered as a complex of active cooperating functional subsystems that cannot be assigned to on specific cerebral localization. Also, epilepsy must be regarded as a multifactorial condition. These many different aspects implicate a plethora of possible relationships between 'epileptic factors' and memory systems. The literature suggests that disease related factors as etiology, age at onset, and localization of the electroclinical focus to be most strongly related to memory deficits in patients with epilepsy. Furthermore, the unique contribution of clinical seizure related factors as type of seizures, seizure frequency, duration of epilepsy, AED medication, and memory functions seems to be less strong. As a consequence, most researches have concentrated on one or a few different aspects, and

systematic research of the prevalence, manifestation and etiology of memory problems in patients with epilepsy, and the influence of the epileptic factors on memory has been sparse. Ossetin (1988) therefore suggests the use of multiple neuropsychological tests in order to investigate memory functions.

Based on these arguments, research has to focus on the relative contribution of each separate 'epilepsy-related' factor. However, these factors are often associated, e.g. the duration of epilepsy is associated with a longer duration of the use of medication and also with age at onset.

NEUROPSYCHOLOGICAL ASSESSMENT IN EPILEPSY

Neuropsychological assessment is a standardized way of enhancing observations. With this, self-reports by the patients or their relatives and clinical observations by the neurologist can be confirmed psychometrically. To do so, we use an individualized, hypothesis-testing assessment approach (Lezak, 1995; Vanderploeg, 2000). We use composite batteries of tests that are presented in a formalized way but with qualitative interpretations of performances; the pattern of test results being just as important as the test scores. Test results must be interpreted within the context of the relationships between behaviour and cerebral functioning.

The initial goal of neuropsychological assessment was the differential diagnosis of organic versus functional disorders. At present, the development of neuroimaging techniques such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET), magneto-encephalography (MEG), etc. has had a significant impact on clinical neuropsychology. Nevertheless, the most sensitive measure of cerebral dysfunction is still behaviour, especially in epilepsy, so neuropsychological assessment remains an important diagnostic tool. Secondly, a neuropsychological assessment is used to direct patient care and rehabilitation, providing information about the possible effects of treatment, e.g. the effects of antiepileptic medication or surgical interventions.

Neuropsychological assessment of memory functions in patients with epilepsy

The measurement of memory functions must firstly reflect the theoretical structure of memory. This implicates that a neuropsychological battery for memory should include

measurements of verbal and non-verbal information and tests of short- and long-term recall, learning and recognition. An international, widely used test battery form memory functions is the revised Wechsler Memory Scale (WMS-r) (Wechsler, 1987). The WMS-r consists of several subtests and provides a broad evaluation of short-term verbal and non-verbal memory and attentional skills. Furthermore, a compound index for long-term memory is provided. Moore and Baker (1997) investigated the psychometric properties of the WMS-r in patients with epilepsy who were candidates for temporal lobe surgery, and identified indications for a verbal memory factor, a visual memory factor and a factor that reflects attentional processes. In time with other reports, they noticed that it is difficult to develop tasks that measure only non-verbal memory.

None the less, there are still a few short-comings. In the WMS-r there are no tasks for recognition. Also, it is not possible to make a qualitative analysis of learning characteristics such as learning rate, rate of forgetting and semantic clustering. For these reasons in our assessment we included a verbal learning test (Verbale Leer en Geheugen Test -VLGT, Mulder, Dekker, & Dekker, 1996), which is originally based on the California Verbal Learning Test (Delis, Kramer, Kaplan & Ober, 1987) and recognition tests for words and figures and rhythm discrimination from the FePsy-battery (Alpherts & Aldenkamp, 1990). In addition, tests for simple reaction time measurement, finger tapping, vigilance and visual searching task of the FePsy battery are also included. Although computerized tests will never replace the qualitative aspects of paper and pencil testing procedure, they can have advantage as additive components of a neuropsychological assessment battery. Technically, the stimuli are always presented in the same way and the responses of the patients are scored and stored automatically. This may be of particular importance with testing the effects of antiepileptic drugs. An advantage of FePsy that specifically accounts for the diagnostic procedures in patients with epilepsy is the possibility of linking the presentation of the tests with EEG/video recording and finding out if epileptic discharges have an effect on cognitive function. The most important disadvantage of computerized psychological assessment is that these highly standardized quantitative testing procedures do not analyze the qualitative behavioural aspects of how responses come about. The complexity of the assessment of brain-behaviour relationships requires an integration of the strengths of both techniques and the theoretical contributions. A neuropsychological assessment must adapt to the patient, and not the other way around.

Finally, we included a memory questionnaire to assess the kind of memory problems that occur in everyday life (Vermeulen, Aldenkamp, & Alpherts, 1993).
Memory functions cannot be assessed in isolation from adjacent cognitive functions, especially those that are also mediated by the temporal lobes, such as language functions in the left hemisphere and visual spatial functions in the right hemisphere. Within the domain of language we examine aspects such as naming, word fluency, vocabulary and lateralization. With regard to visual spatial functions, tests for visual spatial perception and scanning are included, as well as tests for visual constructive abilities such as object assembly and drawing.

Concentration or attentional deficits may lead to memory difficulties in daily life. If the attention span is too short, if patients are incapable of processing information in parallel or if they are very susceptible to interference, then information is stored less well. Also, non-cognitive functions such as personality traits and mood may have an impact on memory function or neuropsychological test performance (Deutsch, Saykin, & Sperlin, 1996). For this reason we included some personality questionnaires. In the epilepsy centres in the Netherlands there is agreement on the neuropsychological test battery for patients with epilepsy who are referred for memory problems (Table 2.1).

When discussing the results of neuropsychological assessment with the patients and their relatives, we should consider the worries that patients sometimes have about memory impairment as a first sign of dementia. Moreover, many patients relate or associate their memory problems with their antiepileptic medication. If the conclusions of the neuropsychological tests show that the memory complaints are based on clear memory deficits that are associated with brain dysfunction, then a memory rehabilitation program in which the use of compensatory strategies is facilitated to support these problems can be offered (Hendriks, 2001; Aldenkamp, Hendriks, & Vermeulen, 1999). However, this does not implicate that if the complaints are not caused by a cerebral dysfunction that a treatment is not indicated. Memory complaints should always be taken seriously; the cause just directs the treatment approach. The impact of the memory complaints on daily life also depends on the patient's everyday activities or the demands that the patient faces in a job or at school.

Table 2.1:

Neuropsychological test battery for patients with epilepsy and memory complaints

DOMAIN	ASPECT[a]	TEST[b]
Intelligence		Wechsler Adult Intelligence Scale (WAIS)
Memory functions	Verbal STM	Digit span (WAIS)
		Simultaneous word recognition (FePsy)
		Verbal Memory index WMS-r
		Verbale Leer en Geheugen Test (VLGT)
	Verbal LTM	Delayed recall verbal subtests WMS-r
		Delayed recall Verbale Leer en Geheugen Test
		Subtest Information WAIS
		Subtest Vocabulary WAIS
	Non-verbal STM	Simultaneous Figure Recognition (FePsy)
		Seashore Rhythm (FePsy)
		Visual Memory index WMS-r
	Non-verbal LTM	Delayed recall non-verbal subtests WMS-r
		Delayed recall Complex Figure Test –Rey
	Metamemory	Memory questionnaire
Language	Word knowledge	Subtest Vocabulary WAIS
	Verbal fluency	UNKA-test
	Lateralization	Dichotic listening
Visual constructive abilities	Perception	Subtest Picture Completion WAIS
		Visual searching (FePsy)
	Construction	Subtest Block Design WAIS
		Subtest Object Assembly WAIS
	Drawing	Complex Figure Test of Rey
Attention & Concentration	Attention	Simple auditive reaction time (FePsy)
	Focused attention	Stroop colour word test
	Divided attention	Trail Making Test
	Sustained attention	Vigilance (FePSy)
Motor functions	Tapping	Tapping (FePsy)

([a]STM, short-term memory; LTM, long-term memory;

[b]WMS-r, Wechsler Memory Scale-Revised)

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CHAPTER 3

Memory Complaints in Medically Refractory Epilepsy: Relationship to Epilepsy-related Factors

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ABSTRACT

This study reports the results are presented of a multicentre study on memory complaints in 252 patients with epilepsy who presented with subjective complaints about memory problems in daily life. Memory complaints were measured with a standardised memory questionnaire (GKLE).

The main purpose was to analyse the type of memory complaints and to examine the relationship between subjective complaints and several epilepsy related factors. These include seizure type, lateralisation and location of the focus, etiology, duration, age at onset, and antiepileptic medication.

As expected patients experienced significantly more memory complaints. In particular, patients of older age and a higher intelligence level complain more about their memory functioning. Although the clinical significance is marginal, neuroticism showed a significant relationship to the total complaint score.

The total amount of subjective complaints is not related to the localisation or lateralisation of the epileptic disturbances. Patients with a longer duration of epilepsy complained significantly more about memory problems, especially about retrieving information from memory. All other epilepsy related factors showed no relationship to memory complaints.

INTRODUCTION

Patients with epilepsy perceive their memory status to be worse than controls (1,2). Thompson and Corcoran (3) performed a survey in 760 epilepsy patients and reported that 54% (compared to 23% in a control group) described their memory functions as a moderate or severe limitation in daily functioning (3). The types of problems reported by the patients were similar to those among controls, but the frequency of complaints was significantly higher in the epilepsy population. The most outstanding problem reported by the patients with epilepsy was the 'tip of the tongue phenomenon'.

The prevalence of memory problems in patients with refractory epilepsy has been estimated as 20-50% (4). In another study the authors describe that more than half of the patients who were referred for neuropsychological assessment reported memory difficulties (5).

Although in clinical practice memory complaints have to be taken seriously, if only because of their frequency, they do not necessarily reflect memory deficits as defined by objective neuropsychological assessment (6). In fact, only moderate correlations (i.e. in the range of 0.30-0.40) have been found between self-reported memory complaints and neuropsychological test results (7). Several reasons have been suggested for this discrepancy (6, 8). For example the ecological validity of neuropsychological tests may still be insufficient, or subjective memory problems are easily recognised in daily life and mixed up as a consequence with other underlying cognitive dysfunctions such as attentional deficits. In another study it was found that patients with epilepsy describe more memory complaints than actual deficits on memory tests and suggested that this may be related to a personality factor, neuroticism (2). Recently, it was also concluded that an inverse relationship exist between neuroticism and subjective cognitive complaining (9). As a consequence, patients may overestimate their memory difficulties in daily life. Not only neuroticism but also depression may be related to a high rate of subjective memory complaints (10). More recently, it has been suggested that depression plays an important role in the possible mediating role of self-knowledge and self-belief in one's own memory function, called metamemory, in patients with temporal lobe epilepsy (11). In this latter study more depression is reported in the patient group than in the control group. Those patients who reported to be more depressed underestimated their memory function, although their actual memory performances with

neuropsychological testing did not differ from those patients who did not indicate that they were depressed.

Although subjective memory complaints may be an important sign for the clinician who treats people with epilepsy we must thus conclude that, as yet, it is difficult to interpret such complaints and it is clear that they can not be accepted at face value. A more systematic analysis of such complaints and its relationship to epilepsy and other factors such as personality and mood is therefore imperative.

The aim of our study was to analyse the type of memory complaints and to examine the relationship between subjective memory complaints, and several clinical epilepsy factors; including seizure type, lateralisation and location of the electroclincial focus, etiology, duration, age at onset, and antiepileptic medication.

SUBJECTS AND METHOD

Subjects

Two hundred fifty-two patients with medically refractory seizures were included in a collaborative study among the three epilepsy centres in the Netherlands (Hans Berger Clinic, Epilepsy centre Kempenhaeghe, and SEIN).

Patients were considered for inclusion in this study if they met the following criteria:

1. Subjective memory complaints; experiencing memory problems in daily living;
2. Age between 16 and 60 years;
3. A Wechsler Full Scale intelligence quotient > 80 (12);
4. No signs for clinical depression or aphasia;
5. No indication for a progressive neuropathological condition;
6. No history of status epilepticus;
7. No seizures within 24 hours before neuropsychological assessment.

Within the context of a neuropsychological assessment all patients completed a memory questionnaire for patients with epilepsy, the GKLE (Geheugen Klachten Lijst voor Epilepsie),

that has been described elsewhere (2). Subjects gave estimates of forgetting on 23 questions concerning everyday memory problems, on a 7-point scale, where 1 refers to a minimum and 7 to a maximum of experienced memory problems. A total score can be computed and based on factor analysis, five subscales were constructed. The internal consistency (Cronbach's α) of all items is 0.86, and of the subscales between 0.70 and 0.80. Finally, all patients completed a Dutch personality questionnaire (Amsterdamse Biografische Vragenlijst, ABV) derived form the Maudsley personality inventory, to assess psychoneurotic complaints (13).

Demographic and relevant medical history characteristics of the patients are provided in Table 3.1.

The patient group consisted of slightly more men (55.2 %) than women (44.8%). Most patients were right-handed (85.3%), and the remainder were left-handers (11.5%) or ambidextrous (3.2%).

The majority of patients had partial seizures (80.3%), and only 52 patients (20.7%) had primary generalised seizures. Of the total population 70.2% had complex partial seizures, and 64 patients (25.4%) had secondary generalised seizures.

EEG-registrations showed a temporal localisation in 84.9% or 214 patients. In the other patients seizures originated from the frontal (N=10 or 4%), or the parietal lobe (N=4 or 1%), and in 26 patients (10.1%) no localisation could be made. On the basis of EEG-registrations, the seizures tended to originate from the left hemisphere in 119 patients (47.2%), and from the right side of the brain in 81 (32.1%) patients.

One hundred sixty-seven subjects (66.3%) underwent a MRI-scan, which showed no pathology in 34 (20.4%) patients. Brain pathology was located, this was located in the temporal lobes in 121 (72.5%) cases. In 76 patients (45.5%) the MRI scan lateralised to the left, and in 51 patients (30.5%) pathology was observed in the right hemisphere.

At the time of the neuropsychological assessment, patients averaged 36.39 years of age. In general, their seizure onset was at a mean age of 16.03 years (SD=10.14) and the total number of years with active seizures was 16.18 (SD=11.28).

The majority of these patients therefore may be characterized as suffering from a refractory, localized related epilepsy of temporal origin with complex partial seizures as the dominant seizure type.

Table 3.1:

Characteristics of the Sample (N=252)

Gender	Male	139	55,2%
	Female	113	44,8%
Age, in years		36,39 (10,54)	
Hand preference	Right	215	85,3%
	Left	29	11,5%
	Ambidextrous	8	3,2%
WAIS	Full scale IQ[a]	108,09 (13,91)	
	Verbal IQ	105,81 (14.82)	
	Performance IQ	110,04 (14,01)	
Type of seizures[b]	Generalised absences	11	4,4%
	Generalised tonic-clonic	41	16,3%
	Simple partial	34	13,5%
	Complex partial	177	70,2%
	Secondary generalised	64	25,4%
Localisation seizures	Temporal	214	84,9%
	Parietal	4	1%
	Frontal	10	4%
	No localisation/diffuse	26	10,1%
Lateralisation seizures	Left	119	47,2%
	Right	81	32,1%
MRI-scan (N=167)	No pathology	34	20,4%
	Temporal	121	72,5%
	Frontal	7	4,2%
	Parietal	4	2,3%
	Occipital	1	0,6%
Etiology	Idiopathic	59	23,4%
	Cryptogenic	82	32,5%
	Symptomatic	111	44,1%
AED medication	No medication	27	10,7%
	Mono-therapy	108	42,8%
	Poly-therapy	117	46,5%
Age at Seizure onset [a]		16,03 (10,14)	
Duration of Epilepsy[a]		16,18 (11,28)	
Seizure Frequency per year[a]		222,74 (378,16)	

[a] *SD in parentheses;*

[b] *Total > 252; patients may have multiple seizure types)*

Data analysis

All data were analysed using SPSS 9.0 for Windows (14).

First, a factor analysis was performed on the memory questionnaire to control for interrelations between the items (2). Analysis of variance (ANOVA) was carried out to examine group differences.

Furthermore, multiple analysis of variance (MANOVA) was performed to investigate relationships between the results of the memory questionnaire, several clinical epilepsy factors and results of the personality inventory. Finally, a linear regression procedure was carried out to examine predictors that underlie subjective memory complaints.

RESULTS

Table 3.2 summarises the mean scores and standard deviations for the memory questionnaire and the personality questionnaire.

Table 3.2:

Mean performance, on memory questionnaire (GKLE) and the personality questionnaire (ABV).

ABV	Neuroticism	59,86 (25,08)[a]
	Neurosomatic complaints	21,43 (7,43)
GKLE [b]	Total score (ALL)	85,23 (23,22)
	Absentmindedness (ABS)	19,75 (7,69)
	Memory for Semantic Structures (M)	20,76 (6,13)
	Retrieval (RET)	15,95 (5,24)
	Rote Memory (ROTE)	19,37 (5,88)
	Childhood Memories (CHI)	12,40 (5,63)

([a] SD in parentheses;

[b] higher scores means more memory complaints)

Table 3.3 lists the five areas with most frequent complaints and the five areas with least frequent complaints in the investigated patients. The most frequent complaints involved difficulties in retrieving information from declarative memory, while the least frequent problems concerned remembering information from childhood and attentional problems (distraction).

Table 3.3:

Five most and least frequently experienced memory problems.

Items patients complained *most* frequently about		
1. Being unable to remember a joke, an experience or a story	4,58	(1,68)[a]
2. Not remembering where you saw a film actor before	4,58	(1,67)
3. Forget names of people met at social occasions	4,43	(1,80)
4. 'Tip of the tongue' experience	4,30	(1,57)
5. Forget directions to unfamiliar place	4,06	(1,98)
Items they complained *less* about		
1. Remembering being punished by your parents as a child	3,35	(2,08)
2. Remembering a trip you took as a child	3,32	(1,93)
3. Forget where you put a book or a newspaper	3,09	(1,67)
4. Start with different activity after distraction	3,07	(1,67)
5. Remembering any child you used to play with as a child	2,16	(1,58)

([a] Mean, SD in parentheses)

The internal structure of the list (correlation between items/subscales) was evaluated using a principal factor analysis with varimax rotation. Six factors were extracted, accounting for 57 % of the variance. In interpreting the factors, loadings below 0.40 were disregarded. The first factor (explaining 15.7% of the total variation), reflects problems that can be

characterized as 'absentminded behaviour'. Examples of memory complaints are: 'forgetting where they put a book or a newspaper', or 'often have to check one's pockets to find something', or 'leaving things behind they intended to bring'.

The second factor, (explaining 13.7% of the variance), is represented by questions that refer to problems in 'retrieving information from memory'. Examples of questions that load high on this factor are: 'names or other facts about people one is familiar with, such as telephone numbers or addresses'. Factor three can be interpreted as 'Rote memory' (explaining 9.5% of the variance). This factor reflects problems that can be characterized as the conditional circumstances in which information has to be learned to reproduce it by rote. Examples of questions are 'being distracted by other activities', and 'forgetting why you went to a room'. Also, 'tip of the tongue experiences' has a moderate loading on this factor. The fourth factor (explaining 9.1% of the total variance) consists of items that can be regarded as childhood memories. Typical difficulties that have a unique loading on this factor are: 'remembering a piece of clothing one had as a child', or 'a trip they took as a child'. The fifth factor can be characterised as 'Memory for Semantic Structures' (explaining 9% of the total variance). Examples of memory difficulties that have a unique loading on this factor are: 'remembering a joke', 'an experience or a story', 'remembering the content of a book', and 'remembering what has been told'. Problems in the recollection of the sequence of events of some years ago also show a moderate loading on the first factor described.

This factor structure, showing that the list has five unique subscales concurs, with an earlier analysis of the scale in a similar population (2) on this test shows. We therefore compared our study group with the results of the non-neurological group in the latter study (Table 3.4).

Patients with epilepsy in our study complain significantly more about their memory. This is shown both by the mean total scores and for the scores on the subscales of the memory questionnaire. In our sample patients had an overall score that is about one standard deviation higher than that of normal controls. In general this is considered as a large difference (15). Moreover the patients in our study also reported to more difficulties the subscales Absentmindedness, Memory for Semantic Structures, and Retrieval. On the factor Rote Memory the difference was smaller i.e. 0.5 SD, and on problems concerning Childhood Memory this difference is even smaller.

Table 3.4:

Subjective memory complaints.

	Controls (N=111)[a]	Epilepsy patients (N=252)	p
Total score	71,99 (15,97)[b]	85,23 (23,22)	.000
Absentmindedness	17,76 (4,80)	19,75 (7,69)	.000
Memory for Semantic Structures	15,94 (4.63)	20,76 (6,13)	.000
Retrieval	12,58 (3.98)	15,95 (5,24)	.000
Rote Memory	14,39 (4.80)	19,37 (5,88)	.000
Childhood Memory	11,68 (4.69)	12,40 (5,63)	.042

([a] reference 2;
[b]SD in parentheses)

Correlations with clinical variables

Correlations (Pearson r) were computed between memory complaints (total complaint/subscale scores) and the demographic variables age, sex, education, and IQ. Statistically significant although modest correlations were noted between age and the total score (r = 0.19), and between age and the subscales Absentmindedness (r = 0.21), and Retrieval (r = 0.23), indicating that those patients who are older had more memory complaints in general, especially with respect to absentmindedness and retrieval.

Table 3.5 summarises the scores for type of epilepsy, dividing the total group into patients with left/right temporal epilepsy, patients with bilateral foci in the temporal lobe, and patients with extratemporal epileptic foci. One-way ANOVA and post-hoc *t*-test comparisons (using Bonferonni procedures) revealed no significant differences for the total amount of complaints or the different subscales between the groups.

Table 3.5:

Memory complaints in four epilepsy groups and univariate F values.

	Extra temp N=26	Left temp N=116	Right temp N=78	Bilat temp N=20	F	p
Total score[a]	87,20 (24,42)	84,34 (24,86)	84,96 (20,54)	87,58 (21,72)	.221	.882
Absentmindedness	20,71 (8,89)	19,12 (7,72)	19,80 (7,12)	21,26 (7,01)	.715	.544
Mem Sem. Struct.	20,66 (6,26)	20,59 (6,58)	20,79 (5,47)	21,95 (5,82)	.271	.846
Retrieval	15,90 (4,82)	15,81 (5,41)	16,03 (5,11)	16,58 (5,93)	.124	.946
Rote Memory	16,46 (6,18)	16,56 (6,06)	16,32 (5,41)	15,26 (6,23)	.268	.848
Childhood Memory	13,46 (6,00)	12,26 (5,76)	12,03 (5,28)	12,53 (5,53)	.623	.601

([a] Mean, SD in parentheses)

Table 3.6 is the multivariate analysis of variance (MANOVA) for the total score and the five subscales as dependent variables and the remaining epilepsy-related factors - antiepileptic drugs, age at onset, duration, etiology, and type of seizures- as independent variables. This revealed significant differences on the total complaint score ($F\ 3.486\ P < 0.05$) and the subscale Retrieval ($F\ 3.961$, $P < 0.05$), for the factor duration of epilepsy. Patients with a longer duration of epilepsy complained significantly more about memory problems, especially about retrieving information that was once stored in memory. All the other epilepsy-related factors showed no significant effects on the memory questionnaire.

Table 3.6:

F values, MANOVAs, Total complaint and subscale scores, for epilepsy-related subpopulations

	AED	Seizure Type	Etiology	Duration	Age at onset
Total score	0.230	0.760	1.121	3.486[a]	0.282
Absentmindedness	0.001	1.269	0.580	2.476	0.003
Mem for Sem Struc	1.570	0.943	0.960	2.757	0.113
Retrieval	0.019	0.371	2.287	3.961[a]	0.004
Rote Memory	1.281	0.508	0.098	2.775	0.017
Childhood Memory	0.612	0.531	1.291	0.806	0.513

([a] $p < 0.05$)

Finally, we computed correlations between the total complaint score and the five subscales of the memory questionnaire, and the scores on the personality test.
The total complaint score, although significant, was weakly correlated to Neuroticism (r=0.14) and Neurosomatic Complaints (r=0.19). Furthermore, Neuroticism and Neurosomatic complaints were significantly correlated with Memory for Semantic structures (r = 0.16; r = 0.30). Also, Rote Memory is correlated significantly with Neurosomatic complaints (r = 0.17).

To explore which clinical or demographic variables can predict the results on the memory questionnaires we performed a stepwise linear regression analysis (Table 3.7).

Table 3.7:

Linear Regression analysis with memory questionnaire; Total score and subscales scores as dependent variables (R^2> 15%)

	R^2 (cumulative)	F-values	P
Total memory complaint score			
Step 1: Neurosomatic complaints	.113	.336	.000
Step 2: Age	.179	.256	.002
Step 3: total IQ	.222	.213	.01
Absentmindedness			
Step 1: Neuroticism	.060	.245	.005
Step 2: total IQ	.124	.255	.003
Memory for semantic structures			
Step 1: Neurosomatic complaints	.212	.460	.000

Relations were interpreted only when the regression model explained more than 15% of the variance (R^2 > 15%).

For the total memory score, three variables are included in the regression model. In the first step Neurosomatic Complaints is included, which explains 11% of the variance. Age and total IQ are included in the second and third steps. The three variables combined explain almost 23% of the variance which is relatively modest. The relationship can be interpreted as follows: persons with higher neuroticism, older age and higher intelligence tend to complain more about memory problems. Remarkably epilepsy-related factors do not contribute to the degree of memory complaints patients have in daily life. Neuroticism is the first included variable for the subscale Absentmindedness, but explains only 6% of the variance. The subscale Memory for Semantic structures is explained only by the variable Neurosomatic Complaints, which counts for 21 % of the variance. Also, Retrieval is explained only by one variable. Age explains 11% of the total variance.

DISCUSSION

As part of a multicentre study on memory problems in patients with epilepsy, subjective memory complaints were analysed. Patients with medically intractable epilepsy who had subjective complaints about memory problems in their daily life were included. Interestingly, only about 21% of them seemed to have primary generalised seizures. All other patients (79%) have any type of partial seizures, and 70% of the total population had complex partial seizures. Based on EEG registration about 85% of the total research population showed a temporal localisation of the seizures. Among those with partial seizures, the epileptiform discharges originated in the left hemisphere in 60%, whereas in the other patients these started on the right side of the brain. Although only two-thirds of all patients underwent a MRI scans, the majority (i.e., 121 patients) showed pathology, if any, in the temporal lobes that lateralised in 63% of the cases to the left side of the brain and in 37% to the right side. The average duration of the epilepsy (i.e., number of years during which seizures occurred) was more than 16 years.

Using subjective memory complaints as an inclusion criterion, it is remarkable, and possibly of relevance for determining who is at risk, that our study group consisted mainly of patients with a chronic refractory localised related epilepsy of (left) temporal origin. This concurs with the expected risk group, given the critical function of temporal brain structures for memory (16).

For the measurement of subjective memory complaints a standardized memory questionnaire was used (2). The scale comprised five subscales in our patient group, using factor analysis: Absentmindedness, Memory for Semantic Structures, Retrieval, Rote Memory, and Childhood Memories. This is similar to the result of the former study with this memory questionnaire. The patients with epilepsy in this study reported about one standard deviation more memory problems than normal controls. Large differences were also found on the subscales Memory for Semantic Structures, Retrieval and Absentmindedness. The memory complaints of the patients with epilepsy in this study can thus be characterised as reflecting primarily problems in absentminded behaviour and the retrieval of complex meaningful information. This indicates that we may expect an overrepresentation of these types of complaints in clinical practice.

Analysis of relationships with both demographic and clinical variables showed that a

significant correlation exists between memory complaints and the personality factors neuroticism and neurosomatic complaints, age and duration of epilepsy. As factors may be intercorrelated (as, for example, age and duration of epilepsy) a regression analysis was carried out. This confirmed the importance of neuroticism and age and added intelligence level as an important variable. This relationship shows that with older age and higher IQ and especially with more emotional problems in the area of neuroticism, there is an increasing tendency to present memory complaints. The impact of these three factors is even more prominent, as we excluded patients with high age (> 60 years), low IQ (Full scale IQ < 80), or clinical depression. Remarkably, there were no significant relationships between characteristics of epilepsy and memory complaints, other than the aforementioned general characteristics of this population. In this study we did not find a relationship between memory complaints and other general demographic variables as gender and level of education. After analysis of the relationship between epilepsy related factors and memory complaints in more detail, several comments can be made.

First, no significant differences were noted between patients with a left, right, or bilateral temporal foci and patients with an epileptic focus in extratemporal regions. This is in agreement with the results of a recent study on the outcome variables that may influence the subjective cognitive functioning of patients with temporal lobe seizures after epilepsy surgery (9). Those authors found that lateralisation was not a significant predictor of subjective memory functioning. However, this is not in agreement with results described in early studies with patients who underwent temporal lobectomies, in which a lateralisation effect has been suggested (17, 18, 19).

It has been suggested that a history of epilepsy is the crucial variable that contributes negatively to self perception of memory functioning (1). Also, the results of our study showed that the more years with seizures, the more memory complaints occur. Interestingly, subjects particularly perceive difficulties with memory problems that reflect the domain of Retrieval. We must however take into account however that this relationship is weak and all other complaint domains showed no significant differences with a longer duration of active epilepsy.

As also reported by Bennet-Levy et al (19) we did not find that age at onset is an important factor in determining subjectively perceived memory problems. However, these results are not concurrent with a study that found that patients with a late seizure onset

complain more about retrieval of verbal information (10).
Although in clinical practice many patients attribute their memory problems to the antiepileptic medication, we could not demonstrate a medication effect, i.e. patients without medication, or on mono- or poly-therapy, did not evaluate their memory problems different. Finally, the different types of seizures of patients in this study did not show any relationship to subjective memory complaints.

In clinical practice referral for neuropsychological assessment is based largely on subjective complaints. Our study showed that the group at increased risk of such complaints consists of patients with refractory epilepsies of temporal origin with a longer period of actual seizures. Retrieval complaints are the dominant complaint in the group. Within this group the predominance of neurotic problems is important. This may reflect the development of psychosocial consequences of having chronic refractory epilepsy. The effects of age and general intelligence were been known previously.

Acknowledgements
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CHAPTER 4

Memory Profiles in Patients with Left or Right Temporal Lobe Epilepsy

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ABSTRACT

We studied different memory profiles in a large sample of 192 patients with intractable seizures originating from the left (N=116) or right (N=76) temporal lobes and subjective memory complaints.

Based on a neuropsychological test battery we aimed at finding memory profiles using the accepted memory subsystems as elements for this high risk population of patients, i.e. Verbal Short Term Memory (VSTM), Verbal Long Term Memory (VLTM), Non verbal Short Term Memory (NvSTM), and Non verbal Long Term Memory (NvLTM).

The results show that patients with left temporal lobe epilepsy (LTE) have a different memory profile and risk pattern for memory deficits, compared to patients with right temporal lobe epilepsy (RTE).

For the LTE group we find impairments in all four memory subsystems (VSTM, VLTM, NvSTM, NvLTM), although verbal memory deficits are most dominant. Compared to the normal population medium to large deviations are found in making verbal associations and the acquisition of episodic verbal information for patients with LTE. We found no systematic deficits of NvSTM and NvLTM in both the LTE and RTE patients. Although this is in line with other studies, we argue that the inconsistent relationship between right TLE and non verbal memory deficits may also be a result of insufficient sensitivity of the measurements used.

INTRODUCTION

In clinical practice, many patients with epilepsy report to experience memory difficulties in daily life[1-7]. Studies have identified temporal lobe epilepsy as the dominant risk factor[8-10]. In particular patients with seizures originating in the left temporal lobe have an increased risk to develop memory problems. In a recent study we have confirmed this relationship[11]. In light of the temporal location of essential structures for memory (such as the hippocampus) this relationship is not surprising[12-14].

Thus far 'memory difficulties' were presented as a homogeneous disorder, whereas cognitive research recognizes memory as an extremely complex system with many subsystems and mechanisms[12,15,16]. Both for clinical research and for clinical practice, it is important to delineate the exact difficulties of the memory subsystems. For research such knowledge would possibly help us to explore the neuronal mechanisms that underlie the memory impairments. For clinical practice it could help us to 'translate' the memory difficulties to complaints that patients have. Numerous studies have shown that patients' complaints do not correlate well with results of psychometric tests[5]. Several reasons have been suggested for this discrepancy, but the lack of knowledge of the impairments in the memory subsystems may lead to inadequate assessments and erroneous interpretations of patients' complaints. It may well be that in stead of standardized test batteries, fine-tuned assessments are needed.

In this study we aimed at finding memory profiles using the accepted memory subsystems as elements for the high risk population of patients with temporal lobe epilepsy: Verbal Short Term Memory (VSTM), Verbal Long Term Memory (VLTM), Non verbal Short Term Memory (NvSTM), and Non verbal Long Term Memory (NvLTM).

Our primary research question was to assess:

- To what extent patients with temporal lobe epilepsy have memory difficulties, compared to the normal population;
- Which of the memory subsystems show impairments;
- Whether there are differences between patients with left-sided temporal lobe epilepsy compared to right-sided temporal lobe epilepsy.

SUBJECTS AND METHOD

Subjects

Patients were considered for inclusion in this study if they met the following criteria:

1. Subjective memory complaints; experiencing memory problems in daily living;
2. Age between 16 and 60 years, because of the effects of normal aging on memory;
3. A Wechsler Full Scale intelligence quotient > 80, to exclude patients with a subnormal intelligence;
4. No signs for clinical depression or aphasia, because the potential interference with memory functions;
5. No indication for a progressive neuropathological condition, such as cerebral tumours, or dementia;
6. No history of status epilepticus;
7. No seizures within 24 hours before neuropsychological assessment.

Two hundred fifty-two patients with epilepsy and subjective memory complaints were consecutively included from the three tertiary referral epilepsy centers in the Netherlands (Epilepsy centre Kempenhaeghe, Heeze; Epilepsy centre Hans Berger Clinic, Breda; SEIN, Heemstede); 192 of these patients had a unilateral epileptic focus in the temporal lobe. Table 4.1 summarizes the main characteristics of the 192 patients with unilateral temporal lobe epilepsy.

We found no statistical differences for age, educational level, gender, and hand preference between the LTE and RTE groups. The group of patients with a LTE has a significant lower mean total IQ, compared to the right (T(-2,88)=0,004). Furthermore age at onset and duration of epilepsy also did not differ significantly between both groups, whereas the LTE patients had a significantly higher seizure frequency (T(-2,23)=0,024).

Table 4.1:

Main characteristics of the patients with left or right temporal lobe epilepsy

	LTE	RTE
No. of patients	116	76
Age, years (sd)	35,62 (9,97)	37,95 (10,27)
Gender (male / female)	66/50	36/40
Hand preference:		
Right / left / ambidextral	97/15/4	66/8/2
Level of education	3,14	3,39
Intelligence:		
WAIS Full scale IQ (sd)	106,43 (14,30)	112,21 (12,51)
WAIS Verbal IQ (sd)	103,14 (15,30)	110,82 (12,71)
WAIS Performance IQ (sd)	110,34 (14,22)	112,00 (13,07)
Epilepsy-factors:		
Age at Seizure onset (sd)	15,03 (10,46)	17,27 (10,54)
Early (<5yrs) / late (>5yrs)	29/87	13/62
Seizure Duration (sd)	18,99 (10,51)	18,97 (10,53)
1-8yrs / 8-30yrs / >30yrs	23/72/21	16/50/10
Seizure Frequency/year (sd)	133,10 (341,85)	83,82 (88,03)
Low / high	51/65	33/43
Etiology:		
Idiopathic / cryptogenic / symptomatic	28/40/48	16/25/35
Type of seizures:		
Generalised absences	2	1
Generalised tonic-clonic	9	11
Simple partial	15	11
Complex partial	88	61
Secondary generalised	34	19
AED medication:		
No medication	16	9
Mono-therapy	33	24
Poly-therapy	67	43

Neuropsychological measures

The test battery has been described elsewhere[12].

- The Wechsler Adult Intelligence Scale (WAIS)[17] for intellectual functioning.
- For the measurement of *memory functions:*
    - The Wechsler Memory Scale-Revised (WMS-R)[18] was administered. The WMS-r contains 13 subtests that measure different subsystems of memory. With the scores of these subtests 5 different indexes can be calculated: General Memory, Visual Memory, Verbal Memory, Attention and Concentration, and Delayed Memory.
    - Furthermore, we used the Verbale Leer en Geheugen Tetst (VLGT)[19] for verbal list learning, which follows the same administration procedure as the California Verbal Learning Test[20]. The requires learning of a list of 16 semantically related concrete words, in five consecutive trials, short term recall after learning an interference list, cued recall, long term recall and recognition after 30 minutes. The parameters of interest were the total number of words over all five learning trials, learning rate, rate of forgetting, consolidation, short and long term retrieval, recognition, and the extent of semantic clustering.

Table 4.2 gives an overview of the different (sub) tests used, as well as the memory subsystems: Verbal Short Term Memory (VSTM), Verbal Long Term Memory (VLTM), Non verbal Short Term Memory (NvSTM), and Non verbal Long Term Memory (NvLTM).

Table 4.2:

Overview of the memory tests used as objective indications for memory systems; Verbal Short Term Memory (VSTM), Verbal Long Term Memory (VLTM), Non verbal Short Term Memory (NvSTM), Non verbal Long Term Memory (NvLTM).

	VERBAL MEMORY	NON VERBAL MEMORY
STM	Digit Span-forwards (WMS-r)	Visual Memory Span-fw (WMS-r)
	Digit Span-backwards (WMS-r)	Visual Memory Span-bw (WMS-r)
	Logical Memory I (WMS-r)	Visual Reproduction I (WMS-r)
	Total List A (VLGT)	
	Retrieval-Short Term (VLGT)	
	Verbal Paired Associates I (WMS-r)	Visual Paired Associates I (WMS-r)
	Learning Rate (VLGT)	
	Semantic Clustering (VLGT)	
LTM	Information (WAIS)	Visual Reproduction II (WMS-r)
	Vocabulary (WAIS)	Visual Paired Associates II (WMS-r)
	Logical Memory II (WMS-r)	
	Verbal Paired Associates II (WMS-r)	
	Consolidation (VLGT)	
	Retrieval-Long term (VLGT)	
	Rate of Forgetting (VLGT)	
	Recognition (VLGT)	

(STM: Short Term Memory; LTM: Long Term Memory)

Statistical analysis

Data were analyzed with the Statistical Packages for the Social Sciences (SPSS) version 9.0 for Windows (Norusis, 1998).

Memory profiles were generated by computing Z-scores for all scores on the memory subtests. This makes standardization of the test scores and a comparison of different tests possible, and to create a clear pattern of memory functions for Verbal STM, Verbal LTM, Non verbal STM, and Non verbal LTM. Each of the scores were transferred to norm scores, to compare the scores with the normal population. The z-score '0' then indicates that no difference exists with the normal population. Deviations of .20, .50 and .80 are seen as small,

medium and large deviations from the normal population in line with the convention proposed by e.g. Cohen (1977).

RESULTS

Table 4.3 presents the results of the analysis.

Table 4.3:

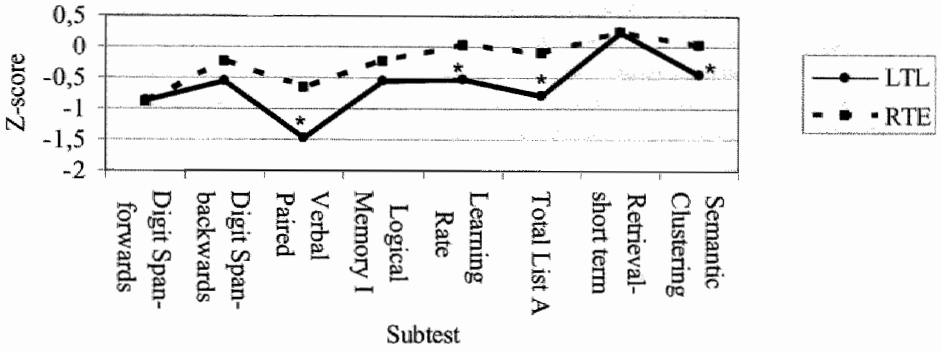
Memory profiles for memory subsystems (VSTM, VLTM, NvSTM, NvLTM) for patients with left (LTE) and right temporal lobe (RTE) epilepsies.

	LTE (N=116)	RTE (N=76)
Verbal Short Term Memory (VSTM)		
Digit Span-forwards	-0,884*	-0,859 *
Digit Span-backwards	-0,557 *	-0,248
Verbal Paired Associates I	-1,462 **	-0,653 *
Logical Memory I	-0,550 *	-0,227
Learning Rate	-0,517 *	0,018
Total List A	-0,782 *	-0,107
Retrieval-short term	0,224	0,241
Semantic Clustering	-0,544*	0,027
Verbal Long Term Memory (VLTM)		
Information	0,107	0,444
Vocabulary	0,160	0,688 *
Verbal Paired Associates II	-1,707 **	-0,488
Logical Memory II	-0,864 *	-0,329
Rate of Forgetting	-0,425	-0,223
Consolidation	-0,638 *	-0,152
Retrieval-long term	-0,167	0,182
Recognition	0,178	-0,277
Non verbal Short Term Memory (NvSTM)		
Visual Memory Span-forwards	-0,525 *	-0,385
Visual Memory Span-backwards	-0,329	-0,319
Visual Reproduction I	0,321	0,376
Visual Paired Associates I	-0,759 *	-0,542 *
Non-Verbal Long Term Memory (NvLTM)		
Visual Reproduction II	-0,286	-0,170
Visual Paired Associates II	-0,317	0,038

(difference ≥ 0.5 SD; ** difference ≥ ± 1.0)*

Results for each memory subsystem were plotted, using the z-scores. A score of 0 is similar to the normal population. Scores below 0 indicate impairment.

Verbal Short Term Memory



(Z-score of 0 is score similar to the average scores in the general population

* indicates statistical differences between left and right temporal lobe epilepsy)

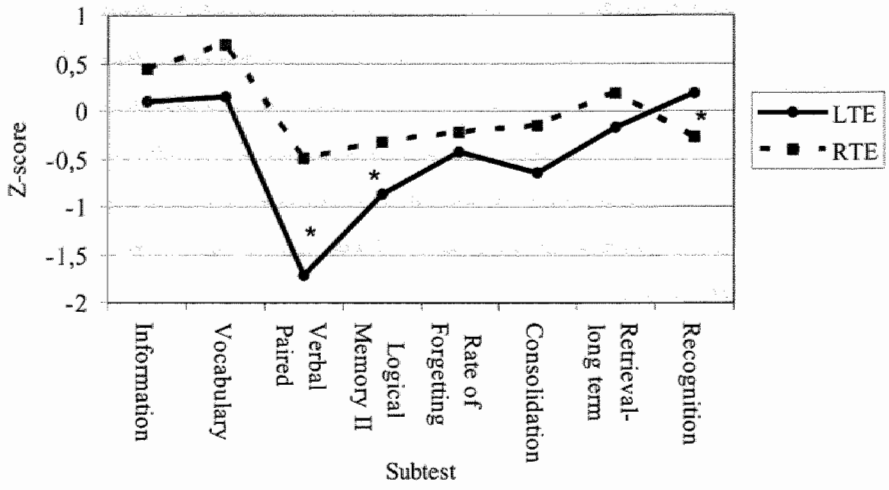
Figure 4.1:

Left versus Right Temporal Lobe patients: Verbal Short Term Memory (VSTM)

Almost all tests for the LTE patients score more than -0.5 sd, from the normal population, whereas Verbal Paired Associates I differs even more than 1 sd. The scores for the RTE patients only deviate with > 0.5 sd for Digit Span forward and Verbal Paired Associates I.

T-testing with Bonferroni correction showed significant differences between the left and right temporal lobe patients, for Verbal Paired Associates I (T(-3.52)=.001), Learning Rate (T(-3.25)=.001), Total List A (T(-4.00)=.000), and Semantic Clustering (T(-3.46)=.001).

Verbal Long Term Memory



(Z-score of 0 is score similar to the average scores in the general population

* indicates statistical differences between left and right temporal lobe epilepsy)

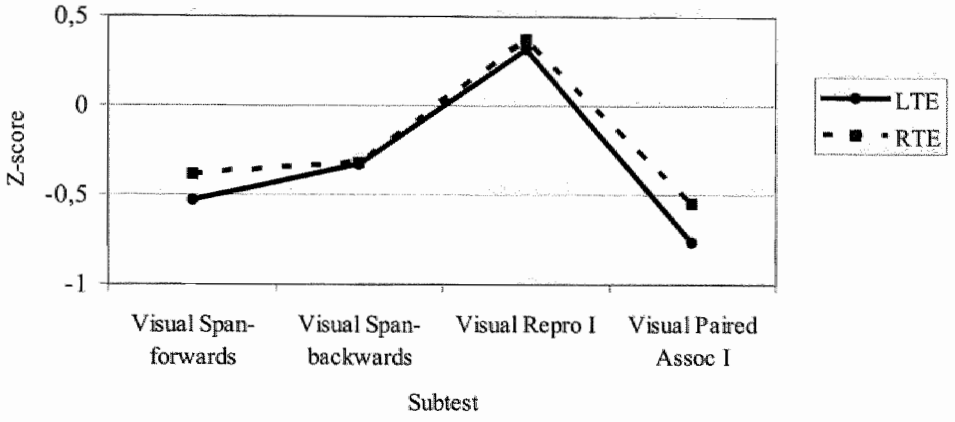
Figure 4.2:

Left versus Right Temporal Lobe patients: Verbal Long Term Memory (VLTM)

Also for long-term verbal memory all Z-scores are lower for the LTE patients, compared to the RTE patients, except 'Recognition'. The score on Verbal Paired Associates II is more than 1 sd below the normal population, while Logical Memory II and Consolidation deviate more than 0.5 sd. Furthermore, the right temporal lobe patients score 0.5 sd above the normal mean on Vocabulary (T(-3.37)=.001) and Information (T(-3.13)=.002).

The left temporal lobe patients score significantly worse on the long term retention of Verbal Paired Associates II (T(-4.78)=.000), and Logical Memory II (T(-4.06)=.000). The right temporal lobe patients score significantly worse on Recognition (T(3.079)=.003) than the Left TL group.

Non verbal Short Term Memory



(Z-score of 0 is score similar to the average scores in the general population

* indicates statistical differences between left and right temporal lobe epilepsy)

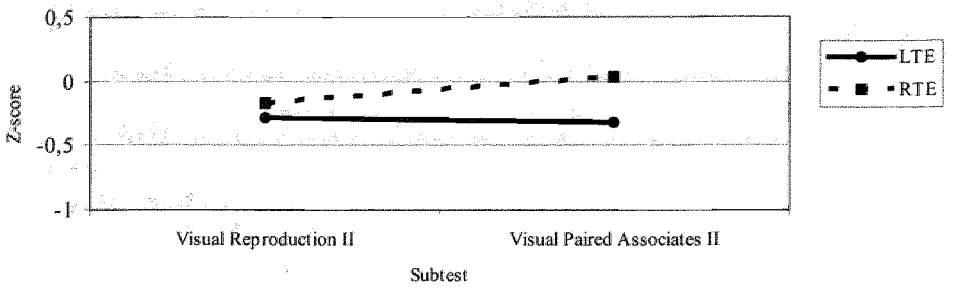
Figure 4.3:

Left versus Right Temporal Lobe patients: Non verbal Short Term Memory (NvSTM)

Figure 4.3 shows that the pattern of scores on the tests for NvSTM is comparable. Both groups perform more than 0.5 sd below the normal population on Visual Paired Associates I, and only the left temporal lobe patients on the forwards reproduction of Visual Memory Span. We have found no statistical significant differences between the left and right temporal lobe patients on tests for non verbal short term memory.

Non verbal Long Term Memory

The scores of both groups on both tests for NvLTM are within the range normal of the normal population. Again, when comparing the scores of the left and right temporal lobe patients, no significant differences are found.



(Z-score of 0 is score similar to the average scores in the general population

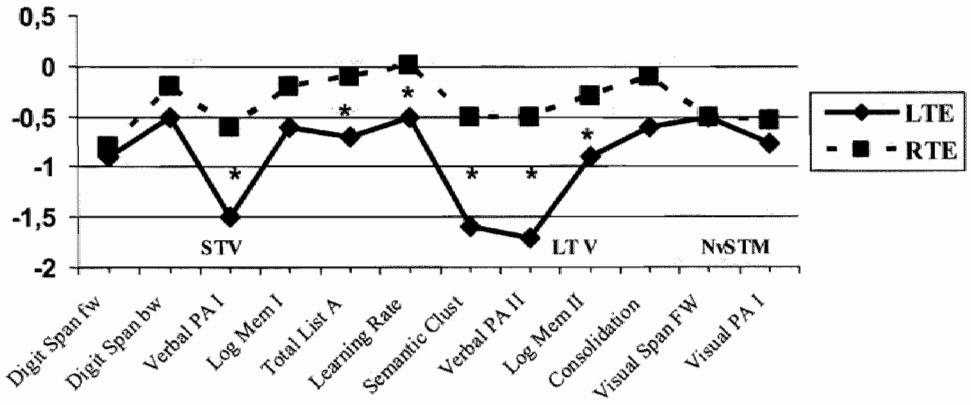
* indicates statistical differences between left and right temporal lobe epilepsy)

Figure 4.4:

Left versus Right Temporal Lobe patients: Non verbal Long Term Memory (NvLTM)

DISCUSSION

Figure 4.5 shows the profile of memory scores for the 12 tests that showed lowest scores compared to the normative scores, i.e. deviate > 0.5 sd from the normal population. These all concern patients with left temporal lobe epilepsy. Right temporal lobe epilepsy obviously does not have a similar risk as only four of the 12 tests show a deviation > 0.5 sd.



(Z-score of 0 is score similar to the average scores in the general population

* indicates statistical differences between left and right temporal lobe epilepsy)

Figure 4.5:

Profile of all memory scores deviating > 0,5 sd from 0 and differences between left and right temporal lobe epilepsy.

So, as expected LTE patients show different memory profiles and risk patterns for memory deficits, compared to RTE in VLTM. Although the pattern of strengths and weaknesses is more or less the same, both groups perform at a different level, with the right temporal lobe patients significantly better than the left temporal lobe group. Furthermore, the patterns of scores for NvLTM are comparable for LTE versus RTE. Considering short term

memory, both groups deviate at a medium level from the normal population, while they perform both within the normal range of the normal population in tests for non verbal long term memory. We also did not found any statistical differences between both groups in the domains of non verbal memory.

If we interpret the profile for the left TLE patients than we may conclude that a negative functional impact on all four memory subsystems (VSTM, VLTM, NvSTM, LvLTM), resulting in a higher risk for developing global memory deficits for patients with a left temporal lobe epilepsy, compared to normal controls and patients with seizures originating in the right temporal structures. However, impairments in verbal memory are the most dominant type of memory impairments in patients with LTE. Almost all tests used for verbal STM score significantly below the mean of the normal population, with medium to large deviations according to the convention of Cohen[22]. Patients with a LTE show specific deficits in making verbal associations and the acquisition of episodic verbal information that is presented auditory within a semantic context. This is in line with earlier research, which suggests that a left TLE interferes with the encoding or consolidation capacity of a memory trace[23,24]. This may reflect a deficit in the storing process of information and possibly a dysfunction of the hippocampal complex, as other studies have shown[25-29].

Similar to other studies we found that patients with a LTE also show significant deficits in clustering the verbal material on their semantic correspondence[9,27,28,30]. Some authors found a significant relationship between an adequate language competence and verbal learning in patients with complex partial seizures from left or right temporal lobe origin, measured with the California Verbal Learning Test[20], the original American version of the Dutch VLGT[19], used in this study. Semantic clustering in the right temporal lobe patients of this study is significantly better than the left TLE and similar to the normal population[9]. Furthermore in agreement with our results, they concluded that patients with complex partial seizures of left temporal lobe origin, showed poorer verbal association and semantic organization in their verbal learning abilities[9,30]. Some studies suggest that deficits in basic language functions underlie impairments in the acquisition of verbal episodic information and semantic organization[31-33]. This remains to be studied; however in this study vocabulary did not score below the mean of the normal population in both groups, although the LTE patients performed significantly worse compared to the right temporal lobe patients indicating a laterality effect as expected.

In this study we have found that the LTE patients scored significantly better on the Recognition index of the VLGT that seems in contrast with most studies[9,32,34]. However, the Recognition index of the VLGT is measured in contrast to the scores on free recall conditions. While the LTE patients (and not the patients with RTE) show significant impairments on the free recall, they simply benefit more from the cues that are given with the recognition condition.

In this study no systematic deficits of non verbal memory are found. This is in fact true for both the left TLE an right TLE group. This is in line with results of many other studies in clinical practice[35,36]. However, this finding is difficult to explain because recent f-MRI studies support the relationship between right temporal lobe structures and non-verbal memory functions[13,26]. Several reasons have been suggested for this inconsistent relationship between right TLE and non-verbal memory deficits. For instance, there is limited knowledge about the exact nature of the memory stimuli for which the right temporal lobe is specialized[37]. By using a sensitive computer paradigm to measure various aspects of spatial memory, we recently found that the right and left mesial temporal lobes are involved differentially in various forms of spatial memory[29]. While patients with right mesial temporal lobe epilepsy were impaired in coordinating positional processing, the patients with left mesial temporal lobe epilepsy showed deficits in the ability to bind together object information to their spatial locations. We used clinically developed tests as the VLGT and WMS-r that are widely accepted in clinical practice and because we included patients with intractable epilepsy who complain about memory failures in daily life. The Wechsler Memory Scale-revised is the most extensively used battery for memory assessment of adults, and more specifically also in specialized epilepsy centers[38,39]. In a study with a sample of intractable epilepsy patients a three-factor structure (visual memory, verbal memory, attention and concentration) that was material specific for the WMS-r was found[40]. However, like the VLGT is a widely used test for verbal learning, in clinical practice there is no test for non verbal learning available. Consequently, in this study we used more measurements for verbal memory than for non verbal memory. This increases the possibility that by chance we will find more significant differences in the domains of verbal memory. In this respect the revision of the WMS-r i.e. the Wechsler Memory Scale III (WMS-III) can be more promising for future clinically orientated research. In a recent study it is concluded the WMS-III is more sensitive to modality-specific memory performance in patients with medically intractable

epilepsy who underwent temporal lobectomy[41]. Two new subtests for non verbal memory (i.e. Faces I, and Family Pictures) significantly discriminated between right and left temporal lobectomy patients. Clinical decisions about the choice of anti-epileptic drug treatment or a surgical treatment are influenced by the patient's subjective judgments of functional deficits. This requires neuropsychological assessment that is often not correlated with the subjective patient complaints. Therefore, efforts to improve the neuropsychological assessment are as worth exploring. Our study shows that a possible approach is to focus more on certain memory subsystems in relationship to characteristics of the epilepsy. This implies that we should ask different questions for patients with a LTE than for other patients.

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CHAPTER 5

Relationships between Epilepsy Related Factors and Memory Impairment

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ABSTRACT

In this study, we will explore the effect of epilepsy-related factors such as: 'type of epilepsy, 'site and side of focus localization' and 'age at onset', as well as four seizure-related factors: 'years with continuing seizures', 'seizure type', 'seizure frequency' and the treatment factor 'adverse effects of the medication', on memory impairment. Additionally, we explored whether these epilepsy factors are related to different aspects of memory i.e., short vs. long-term recall, learning, and verbal vs. nonverbal memory.

252 Patients with epilepsy and subjective memory complaints were consecutively included from the three epilepsy centres in the Netherlands to assess memory functions the Wechsler Memory Scale-Revised (WMS-r), and the Dutch version of the California Verbal Learning Test for verbal list learning, was administered.

MANOVA did not show statistically significant effects of the epilepsy factors on memory for the total study sample. For the patients with a unilateral epileptogenic focus in the temporal lobes, MANOVA showed statistically significant effects of lateralisation, with most impairment for patients with left-temporal lobe epilepsy and, independently, seizure frequency and 'years with seizures'.

We may conclude that epilepsy-related dysfunctions in the temporal lobe are the dominant risk factor for developing memory problems, specifically verbal memory problems (verbal learning and problems consolidating verbal information), with more severe impairments with continuing seizures and when seizure frequency is high.

INTRODUCTION

Memory problems are the most commonly reported cognitive problems in patients with epilepsy (1). Several studies have attempted to find the characteristics of epilepsy that are responsible for this impairment (2,3). Based on a review of the studies that have been published, we have suggested that it is helpful to distinguish the effects of the clinical epilepsy syndrome from seizure-related factors (4,5).

Three characteristics of the clinical epilepsy syndrome are reported to have an effect on memory: 'type of epilepsy', 'localisation of the epileptogenic focus' and 'age at onset': memory impairments have found to be more prevalent in symptomatic and cryptogenic epilepsies, when compared to idiopathic epilepsy (6-9). Patients with temporal-lobe epilepsy are reported to have more memory impairments than patients with extratemporal epilepsies and both groups have more memory impairments than patients with generalized epilepsies (10). In addition, foci in the left temporal lobe are related to verbal memory impairments (2, 11-14). Also, an association between epileptogenic foci in the right temporal lobe and nonverbal memory difficulties have been found, but this relationship is only weak (15-17). An early age of onset was correlated with impaired long-term memory (18). Strauss, et al. (1) examined the contribution of epilepsy-related factors in predicting cognitive impairments including memory, and concluded that age of onset was the best predictor.

Several seizure-related factors are reported to affect memory. Number of years with continuing seizures is associated with memory impairments (19) Although, it might be expected that seizure frequency has some effect, studies show inconsistent results, possibly as an effect of methodological problems (4). Dodrill (20) concludes that, within a population of patients with all kind of seizures, those patients with more than 100 secondary generalized seizures perform less well on tests for intellectual and cognitive functioning, including memory. Seizure type is suggested also to be an important factor as memory impairments have been reported specifically in patients with partial seizures (9, 21) although this has not been confirmed in other studies (22). Finally, a separate treatment-related factor has to be considered, the central side-effects of antiepileptic drugs (AED). For none of the separate drugs convincing effects on memory has been established (23). Polytherapy has, however, found to be associated with memory impairment (9, 24). Conversion of polytherapy to monotherapy may consequently improve cognitive functioning (14). Another study (25)

showed that reducing AEDs improved performance on verbal memory tasks, in a group of medically refractory patients.

Consequently, the most frequent reported factors, with potential effect on memory are 1). Type of epilepsy, 2). Site and side of focus localization and 3). Age at onset, as well as the seizure-related factors 4). Years with continuing seizures, 5). Seizure type, 6). Seizure frequency, and 7). The central adverse effects of the medication. Although these seven factors are undoubtedly correlated, most studies nonetheless have inspected the effects on memory separately for each factor. The relative contribution of the aforementioned epilepsy-related factors combined on memory function has never been studied. The main question in our study is to inspect whether some factors are more important in explaining memory impairment than others. Additionally, we explored whether these epilepsy factors are related to different aspects of memory i.e., short vs. long-term recall, learning, and verbal vs. nonverbal memory.

SUBJECTS AND METHOD

Subjects

Patients with epilepsy were consecutively included from the three epilepsy centres in the Netherlands (Epilepsy Centre Dr. Hans Berger Clinic, Breda; Epilepsy centre Kempenhaeghe, Heeze; SEIN epilepsy centre, Heemstede) in a prospective study during the period 1998-2001. Patients were considered for inclusion in this study if they met the following criteria:

- Subjective memory complaints; experiencing memory problems in daily living;
- Sufficient reasons for a memory assessment according to the clinician;

Both inclusion criteria aimed at including only patients with a higher risk for memory problems; there are both clinical and subjective reasons for memory assessment. The study will therefore only be representative for the 'higher risk patients'.

- Age between 16 and 60 years, to avoid the effects of normal aging on memory;
- A Wechsler Full Scale intelligence quotient > 80, to avoid interfering effects of subnormal intelligence on memory performance;
- No signs for clinical depression or aphasia, because of their interference with memory functions;

- No signs for a progressive neuropathological condition, such as cerebral tumours, or dementia;
- No history of status epilepticus;
- No seizures within 24 hours before neuropsychological assessment (to avoid postictal influence on memory scores): any seizure in the 24 hours preceding the assessment would require a rescheduling of the assessment.

Neuropsychological measures:

- *WAIS*

All patients were assessed with the Wechsler Adult Intelligence Scale (WAIS) (26) with the full-scale IQ, verbal IQ, and performance IQ as variables.

- *WMS-R*

To assess memory functions the Wechsler Memory Scale-Revised (WMS-r) was administered (27). From the WMS-r we used the indices (subscales): General Memory, Visual Memory, Verbal Memory, Attention and Concentration, and Delayed Memory. These tests represent overall memory scores. In addition, the WMS-r subtest scores for working memory, short term verbal and non-verbal memory, and delayed recall were used as variables. These represent more detailed information.

- *VLGT*

Furthermore, the Dutch version of the California Verbal Learning Test (Verbale Leer en Geheugen Tetst, VLGT) (28, 29) for verbal list learning, was administered. This test requires learning of a list of 16 semantically related concrete words, in five consecutive trials, short-term recall after learning an interference list, cued recall, long term recall and recognition after 30 minutes. Results show the total number of words over all five learning trials (Total List A), learning rate, rate of forgetting, consolidation, short and long term retrieval, recognition and semantic clustering.

Statistical analysis

Data were analysed with the Statistical Packages for the Social Sciences (SPSS) version 9.0 for Windows (30). We used a three-step analysis:

In step 1 possible interfering effects of the demographic variables age, gender, educational level and intelligence level on the epilepsy factors were analysed.

In step 2 a multivariate analysis of variance (MANOVA) was performed using a General Linear Model testing the effects on memory of the aforementioned 7 epilepsy-related factors : 'Type of Epilepsy', 'Localization of the epileptogenic focus', 'Age at onset', 'Years with seizures', 'Seizure Type', 'Seizure Frequency' and 'Antiepileptic Medication'.

For possible statistically significant effects the effects of each epilepsy factor separately was subsequently analysed with univariate analysis of variance (ANOVA) was firstly performed with the WMS-r indexes as dependent variables because of their value as overall memory scores. Next the WMS-r subtest scores and VLGT scores were entered as they represent more detailed information.

In step 3, a mediation analysis (31, 32) was carried out, based on the results obtained in step 2 . A mediation analysis will show the type of relationship between epilepsy factors with respect to their effects on memory. Several statistical techniques, including linear regression will be used.

Because previous documented results do not provide us a theoretical model about the causal relations between the epilepsy-related factors and memory, a mediation analysis (31, 32) was used, based on the results of the MANOVAs described in step 1 and 2.

Power-analysis aimed at achieving a sample size sufficient to demonstrate medium-size memory effects. Following Cohen's conventions this was defined as a medium-size effect, i.e. differences of > 0.7 standard deviation with the norm scores on the WMS-r total memory (12 points on the index) (33, 34). The effect size in the power analysis was therefore calculated as the deviation in mean scores from the norm group divided with the pooled standard-deviation, assuming a higher standard deviation in the epilepsy population: $X_i+X_j/\sum sd_{i/i}$: 100-90/15+28/2=0,7 sd Type-1 (α) and type-2 (ß) errors with an effect-size index of 0,7 sd are entered in the power calculation as primary factors. The statistical power is set to $1-\beta=80\%$, and the sensitivity to $\alpha=5\%$ to be able to detect also mild effects. Power analysis consequently sets the required number of patients at 20 patients. However, given the division of the study group into subgroups (see previous variables and statistical model), this requirement is valid for any subgroup. When taking into account the possible subdivisions (see statistical model in the next results section) the total sample size was set at > 250 patients.

RESULTS

In total 252 patients were included. Table 5.1 summarizes the main characteristics of the total sample and separately for subgroups of patients with a left (n=116), or right temporal lobe focus (n=76), a bilateral temporal focus (n=20), or an extra-temporal focus (n=40). Given the characteristics of the sample and the need to sustain power also when the total sample was subdivided in subgroups, the statistical model for the MANOVA could now be quantified into: Memory BY Type of Epilepsy (x3) AND Localisation (x4) AND Age at onset (x2) AND Years with seizures (x3) AND Seizure type (x5) AND Seizure frequency (x2) AND AED-effects (x3).

The number between brackets refers to the subdivision of the total sample into subgroups during the MANOVA procedures:

- Type of epilepsy (x 3: [1] idiopathic generalized epilepsy; [2] cryptogenic localization-related epilepsy; [3] symptomatic localization-related epilepsy).
- Localization of epileptic activity (x 4: [1] left temporal lobe; [2] right temporal lobe; [3] extra-temporal lobe; [4] bilateral temporal).
- Age at onset of seizures (x 2: [1] first seizure before 5 yrs. of age; [2] first seizure after 5 yrs. of age).
- Years with seizures as the number of years with actual seizures (x 3: [1] 1-8 yrs. with seizures; [2] 8-30 yrs. with seizures; [3] more then 30 yrs. with seizures).
- Seizure Type (x 5: [1] generalized absences; [2] generalized tonic-clonic seizures; [3] simple partial seizures; [4] complex partial seizures; [5] secondary generalized seizures).
- Seizure Frequency (x 2: [1] low seizure frequency: <250 absences, or <50 partial seizures, or <10 tonic-clonic seizures per year; [2] high seizure frequency: >250 absences, or >50 partial seizures, or >10 tonic-clonic seizures per year).
- Antiepileptic Medication (x 3: [1] no medication; [2] monotherapy; [3] polytherapy).

Subdivision was based on the relevant factors as identified in the literature as summarized in the introduction and on the requirement to sustain power for each subgroup

Table 5.1:

Main characteristics of the total sample, and patients with Left or Right temporal lobe epilepsy, and an Extra-temporal lobe focus.

	Total	Left Temp	Right Temp	Extra-temp	Bilat Temp
N. patients	252	116	76	40	20
Age, years[a]	36,39 (10,54)	35,62 (9,97)	37,95 (10,27)	35,39 (11,85)	37,00 (12,30)
Gender (male/female)	139/113	66/50	36/40	26/14	11/9
Hand preference:					
right/left/ambidextrous	215/29/8	97/15/4	66/8/2	33/5/2	18/2/0
Level of education (1-7)	3,16	3,14	3,39	3,10	3,11
Age at Seizure onset	15,98 (10,59)	15,03 (10,46)	17,27 (10,54)	15,89 (11,31)	16,88 (10,38)
- early vs. late onset	58/194	29/87	13/62	10/30	14/6
Epilepsy duration	18,70 (11,17)	18,99 (10,51)	18,97 (10,53)	18,00 (13,34)	17,18 (13,46)
- 1-8yrs/8-30yrs/>30yrs	57/151/44	23/72/21	16/50/10	10/23/7	8/6/6
Seizure Frequency/year	157,27 (437,51)	133,10 (341,85)	83,82 (88,03)	393,03 (873,21)	78,14 (121,43)
- low vs. high sz freq	116/136	51/65	33/43	22/18	8/12
Etiology					
idio/crypt/symptomatic	59/82/111	28/40/48	16/25/35	11/13/17	5/4/11
Type of seizures[b]:					
Generalised absences	11	2	1	7	0
Generalised tonic-clonic	41	9	11	17	7
Simple partial	34	15	11	5	0
Complex partial	177	88	61	11	10
Secondary generalised	64	34	19	5	3
AED medication					
No medication	29	16	9	2	2
Mono-therapy	90	33	24	23	9
Poly-therapy	133	67	43	15	9

([a] Mean, SD in parentheses;

[b] Total > 252 patients may have multiple seizure types)

Table 5.2:

Test performances on neuropsychological measurements of the total sample, and patients with Left or Right temporal lobe epilepsy, an Extra-temporal lobe focus, and a Bilateral temporal focus.

	Total	Left Temp	Right Temp	Extra-temp	Bilat Temp
WAIS[a]					
Full scale IQ	108,09 (13,91)	106,43 (14,30)	112,21 (12,51)	106,29 (11,25)	105,58 (18,90)
Verbal IQ	105,81 (14,82)	103,14 (15,30)	110,82 (12,71)	104,88 (13,05)	104,05 (18,88)
Performance IQ	110,04 (14,01)	110,34 (14,22)	112,00 (13,07)	107,15 (12,56)	106,68 (18,17)
WMS-r					
General Memory	93,84 (16,44)	90,17 (16,76)	97,37 (15,16)	97,85 (14,56)	94,11 (19,26)
Verbal Memory	91,54 (16,31)	86,31 (16,10)	97,21 (15,11)	95,70 (14,36)	92,33 (16,99)
Visual Memory	100,50 (16,65)	99,96 (15,97)	100,25 (16,94)	101,67 (16,31)	102,39 (21,22)
Att & Concentration	87,04 (16,04)	86,03 (17,64)	90,07 (13,19)	86,51 (16,24)	82,11 (14,54)
Delayed Recall	91,24 (17,47)	86,86 (17,04)	95,96 (16,34)	96,92 (16,20)	87,11 (19,96)
Logical Memory I (rs)	22,55 (7,54)	21,38 (7,34)	23,95 (8,00)	24,32 (5,98)	20,74 (8,56)
Logical Memory II (rs)	16,47 (8,59)	13,96 (8,04)	19,04 (9,08)	19,38 (7,34)	15,50 (7,99)
Log Mem % retention	70,00 (26,07)	63,34 (27,10)	77,09 (24,28)	76,99 (21,04)	67,42 (26,92)
Verbal Paired Ass I	17,86 (4,15)	16,88 (4,32)	18,92 (3,59)	18,65 (4,25)	18,06 (3,67)
Verbal Paired Ass II	6,77 (1,38)	6,41 (1,57)	7,27 (0,90)	6,95 (1,15)	6,56 (1,54)
Visual Reproduction I	34,19 (5,20)	34,06 (5,38)	34,01 (5,35)	34,87 (4,22)	34,33 (5,66)
Visual Reproduction II	27,77 (9,08)	27,25 (8,98)	27,97 (8,99)	29,60 (9,58)	26,17 (9,04)
Vis Repro % retention	79,70 (20,92)	78,89 (20,99)	81,08 (19,47)	81,76 (24,42)	74,55 (18,26)
Vis Paired Ass I	12,24 (4,31)	12,12 (4,09)	12,50 (4,44)	12,02 (4,82)	12,44 (4,20)
Vis Paired Ass II	5,18 (1,64)	5,08 (1,73)	5,42 (1,68)	5,13 (1,28)	4,89 (1,64)
Digit Span-forwards	6,56 (1,77)	6,63 (1,95)	6,61 (1,61)	6,42 (1,71)	6,17 (1,38)
Digit Span-backwards	5,95 (1,90)	5,77 (1,96)	6,22 (1,74)	6,15 (1,85)	5,61 (2,17)
Vis Mem Span-fw	7,81 (1,85)	7,78 (1,88)	7,89 (1,91)	7,82 (1,92)	7,67 (1,33)
Vis Mem Span-bw	7,18 (1,79)	7,18 (1,88)	7,19 (1,55)	7,05 (2,03)	7,44 (1,62)
VLGT					
Total List A	51,04 (11,87)	47,80 (12,26)	54,71 (9,08)	53,72 (11,06)	52,67 (16,30)
Learning Rate	-0,60 (2,41)	-1,23 (2,44)	0,09 (1,96)	-0,01 (2,54)	-0,33 (2,84)
Rate of Forgetting	0,69 (2,05)	0,86 (2,29)	0,43 (1,46)	0,55 (1,76)	0,83 (2,95)
Consolidation	-0,94 (2,48)	-1,35 (2,73)	-0,33 (2,02)	-0,69 (2,33)	-1,25 (2,26)
Recognition	1,54 (1,92)	0,35 (1,95)	-0,57 (1,81)	0,07 (1,91)	0,03 (1,76)
Retrieval-short term	0,49(2,34)	0,55 (2,41)	0,40 (2,35)	0,31 (2,29)	0,83 (2,04)
Retrieval-long term	0,21 (2,55)	-0,07 (2,81)	0,42 (2,30)	0,28 (2,17)	1,33 (2,27)
Semantic clustering	-0,51 (2,40)	-0,93 (2,51)	-0,03 (2,32)	0,24 (2,01)	-1,33 (2,0)

([a] Mean, SD in parentheses)

Table 5.2 shows the test results on the neuropsychological tests for the total population and for the left or right temporal lobe patients, and patients with an extra-temporal focus separately.

- Step 1: possible interfering effect of demographic variables and IQ-scores

Multivariate analysis of variance (MANOVA) with the epilepsy-related 7 factors as independent variables and demographic variables or IQ-scores as dependent variables yielded no significant multivariate main effects. Apparently the epilepsy-related factors are not confounded by demographic factors or intelligence level.

- Step 2: Effects of epilepsy-related factors on memory performances

MANOVAs with the epilepsy-related factors as the independent variables and the memory test scores (WMS-r indices, WMS-r subtest scores and VLGT indices) as dependent variables also revealed no significant multivariate main effects. Within the total sample of 252 patients with epilepsy we found no statistically significant effects of the epilepsy factors on memory. This finding may however be confounded by the heterogeneity of the sample and the small subgroups of patients with extratemporal foci or bilateral temporal foci. Because of the specific involvement of the temporal lobe structures in memory functions, further analysis was carried out, exclusively for the patients with unilateral temporal focus localization.

- Subgroup of patients with temporal lobe epilepsy

Step 2a: possible interfering effect of demographic variables and IQ-scores

When excluding the patients with extratemporal epilepsy or with bilateral foci 192 patients with seizures originating from either the left or the right temporal lobe remained. Again, as for the total sample, in a first step the possible interfering effects of demographic variables and IQ-scores were inspected. This yielded a significant main effect of 'lateralisation' ($F(6,154) = 3.015$, $p<0.01$).The univariate ANOVAs showed statistically significant lower scores for the patients with a left temporal lobe epilepsy on total IQ ($F(1, 159) = 7.068$, $p<0.01$) and verbal IQ ($F(1, 159) = 10.348$, $p<0.01$).

Furthermore, we found a highly significant main effect of 'years with seizures' ($F(12,308) = 6.899$, $p<0.001$). Post hoc ANOVAs showed a statistically significant lower

educational level in the group of patients with a high number of years with seizures ($F(2,159) = 3.159$, $p<0.01$) .

Step 2b: effects of epilepsy-related factors on memory

MANOVAs with the epilepsy-related factors as the independent variables and the WMS-r indices as dependent variables, yielded a significant main effect of 'lateralisation' ($F(5,151) = 3.244$, $p<0.01$). Univariate ANOVAs showed statistically significant lower scores for the patients with left temporal lobe epilepsy on the WMS-r indices General Memory ($F(1,159) = 5.278$, $p<0.05$), Verbal Memory ($F(1,159) = 10.203$, $p<0.01$), and Delayed Memory ($F(1,159) = 5.570$, $p<0.05$). Secondly, a main effect was found for 'seizure frequency' ($F(5,155) = 2.320$, $p<0.05$). ANOVAs showed statistically significant lower scores for the patients with a high seizure frequency on the WMS-r indexes General Memory ($F(1,159) = 3.977$, $p<0.05$), Verbal Memory $F(1,159) = 4.088$, $p<0.05$), and Attention and Concentration of the WMS-r ($F(1,159) = 4.645$, $p<0.05$). Finally, we found a significant main effect for 'years with seizures' ($F(5,155) = 1.899$, $p<0.05$). ANOVAs showed statistically significant lower scores for the patients with > 30 years with seizures on all WMS-r indexes.

MANOVA for the subtest scores of the WMS-r and the indices of the verbal learning test (VLGT), yielded a significant main effect of Lateralisation ($F(23,89) = 1.684$, $p<0.05$). Univariate ANOVAs showed statistically significant lower scores for the patients with a left temporal lobe epilepsy on the verbal memory test scores: Paired Associations I ($F(1,111) = 12,023$, $p<0.01$), Paired Associations II ($F(1,111) = 16,501$, $p<0.001$), Logical Memory II ($F(1,111) = 6,392$, $p<0.05$), and the retention score of the subtests Logical Memory I and II ($F(1,111) = 6.275$, $p<0.05$), of the WMS-r, as well as for the VLGT scores Total list A ($F(1,111) = 10,190$, $p<0.01$), Learning Rate ($F(1,111) = 7.021$, $p<0.01$), Forgetting Rate ($F(1,111) = 5.045$, $p<0.05$), Consolidation ($F(1,111) = 7.508$, $p<0.01$), and Semantic Clustering ($F(1,111) = 4.661$, $p<0.05$). On one test: Recognition of the VLGT ($F91,111 = 11.633$, $p<0.01$) the patients with a right temporal lobe epilepsy scored lower. Secondly a main effect is found for Type of Epilepsy ($F(46, 178) = 1,518$, $p=<.005$). ANOVAs showed statistically significant lower scores for the patients with a left temporal lobe epilepsy on the indexes Total List A ($F(2,111) = 4,348$, $p<0.05$), Learning Rate ($F(2,111) = 6,007$, $p<0.01$), Consolidation ($F(2,111) = 6,080$, $p<0.01$), and Semantic Clustering ($F(2,111) = 3,634$, $p<0.05$), of the VLGT for verbal learning. This factor therefore duplicates the factor lateralisation.

- Step 3 Mediation-analysis

In the previous step four epilepsy factors were identified with a potential effect on memory: 'Type of epilepsy', 'lateralisation', 'and seizure frequency' and 'years with seizures'. In this analysis we firstly tested whether the effects of Lateralisation (X_1) and Type of Epilepsy (X_2) on memory function (Z) is mediated by seizure frequency (Y_1). The WMS-r indices were used as memory scores. MANOVA only showed a statistically significant main effect of Lateralisation ($F(3,183) = 7{,}017$, $p<0.000$). ANOVA only showed significant results for Verbal Memory ($p=0.001$) and Delayed Recall ($p=0.007$). This confirms that 'Type of epilepsy' here duplicates the effect of lateralisation as the patient with left temporal epilepsy have most impairment. Next we analysed whether Lateralisation and Type of epilepsy have an effect on Seizure Frequency. ANOVA with Seizure Frequency as a dependent variable and Lateralisation and Type of epilepsy as between-subject factors did not show a significant result ($F(5,157) = 1.827$, $p = 0.111$). In the last step, we analysed whether the effect of Lateralisation disappears when Seizure Frequency is used as a covariate. ANCOVA showed that the effect of Lateralisation remains statistically significant ($F(3,154=5.309$, $p=.002$). The results of the mediation analysis therefore show that the effect of Lateralisation on memory is not mediated by Seizure frequency. Lateralisation and Seizure frequency have independent effects on memory; most effects are on Verbal Memory and Delayed Recall.

Next we studied the hypothesis whether the effects of Lateralisation (X_1) and Type of epilepsy (X_2) on Memory functions (Z) are strengthened by Years with Seizures (Y_3), which also showed a significant main effect in the MANOVAs described above. According to the mediation analysis (31) Years with Seizures is considered as a moderator, which is statistically expressed in interaction effects. MANOVA with Lateralisation, Type of epilepsy and Years with seizures as between-subject factors and the WMS-r indices as dependent variables, showed no significant interactions (Lateralisation * Duration: $p=.477$; Type of epilepsy * Duration: $p=.712$; Lateralisation* Type of epilepsy * Duration: $p=.377$). Nevertheless, the former described statistically significant main effect of Lateralisation remains. ANOVA shows that Lateralisation and Type of epilepsy have no significant effect on Years with Seizures ($p=.071$). Years with Seizures therefore cannot be considered as a mediating variable for the effect of lateralisation of focus and the aetiology of epilepsy.

DISCUSSION

Our results can be presented in the following model:

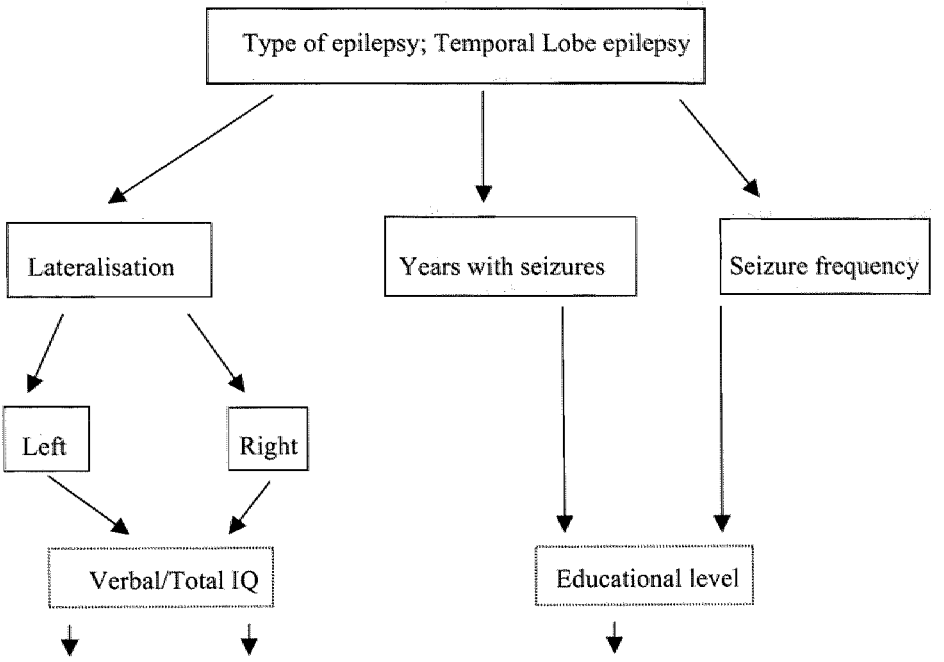

Figure 5.1:

Relationships epilepsy related factors and memory impairment; Final model

This study reconfirms that patients with temporal lobe epilepsy have a substantial increased risk for developing memory impairment (2, 35-39). The study sample consisted of patients consecutively referred because of memory complaints and clinical evidence for memory impairment in daily life. It is remarkable that of the 252 patients included, 212 of these (84%) had temporal lobe epilepsy (with 116 patients with a unilateral left sided focus, 76 with a right sided focus and 20 with a bilateral focus). Moreover most of the patients had refractory epilepsy. This is in line with most clinical studies, showing an increased risk of pharmaco-resistance in temporal lobe epilepsies, especially those originating from mesial temporal structures (40). Within this group lateralisation of the epileptogenic focus is the crucial additional risk factor; i.e. patients with a unilateral left temporal lobe epileptic focus had significantly increased risk of memory impairment, especially impairment of verbal memory and delayed memory. The effect of lateralisation appeared to be independent of other factors influencing memory i.e. 'seizure frequency' and 'years with seizures'. If we look at the subtest scores, patients with a left sided focus have impairments in making long term verbal associations, learning of semantically related verbal information, speed of learning and they show deficits in the consolidation of verbal information (words, verbal associations, and stories).

A second factor that is related with memory impairment is seizure frequency. Looking at the type of tests employed, a high seizure frequency is the only factor that significantly impaired the WMS-r index for Attention and Concentration, which is generally considered as an indication for working memory processes. It may be concluded that a high seizure frequency especially disrupts the first encoding stage of the memory process. Other researchers also have described a relation between a high seizure frequency and such memory dysfunction (9, 20).

Finally, the factor 'continuing seizures', defined as the actual years with seizures, is related to memory impairment. This is in line with the results in other studies (22, 41). This factor was related to verbal memory, nonverbal memory and delayed recall. Although in a previous study (1) it was concluded that the contribution of this factor was weak and unreliable, in our study the effect was independent from other factors.

With respect to the relative contribution of these factors there is a clear hierarchy, with temporal lobe epilepsy as the dominant factor. The patients were not selected on the basis of type of epilepsy, seizure type or aetiology but because they had clinical memory problems as

presented in daily life. This resulted in a study sample consisting almost exclusively of patients with temporal lobe epilepsies. Within this group lateralisation was a second factor with a left-sided epileptogenic focus as the factor explaining a wide range of memory problems, but specifically verbal-oriented problems. These two factors remain the dominant explanation also when the other significant factors ('seizure frequency' and 'years with seizures') were entered in a mediation analysis. In none of the analyses lateralisation lost statistical significance as a main factor. This is in line with previous clinical studies (12, 37) and with the documented function of the temporal lobe for memory function (42, 43). Studies using quantitative MRI-measures have shown that relative loss of neural density in the left mesial temporal lobe regions (i.e. CA3 of the hippocampus) can explain the memory impairment in patients with temporal lobe epilepsy (44, 45). Dysfunction of the hippocampus is also seen as a major trigger for developing refractory epilepsy (40). Our study therefore shows that impairments or functional deficits of temporal lobe structures not only are associated with an increased risk for refractory epilepsy, but also with memory impairment. The extra vulnerability of the left temporal structures may be related to the functional connection with language functions. In line with this, verbal memory functions showed most impairment in relation to left temporal lobe epilepsy. Also the patients with a left temporal lobe epilepsy had a lower verbal IQ. Much is, however, unclear about the effect of left-sided lateralisation. In a quantitative MRI-study (46) diminished neural density in the right hippocampal structures was correlated with nonverbal memory impairments, but clinical studies have failed to find specific nonverbal memory impairments in patients with a right temporal lobe epilepsy, which may be also an effect caused by the instruments used to assess non-verbal memory (17).

The statistical independence of the other two factors: seizure frequency and years with seizures may be commented. Firstly all comparisons in the mediation analysis show that lateralisation (i.e. the dominance of the factor left temporal lobe epilepsy) has a much stronger effect. More important, both factors concern temporal lobe seizures and therefore both factors represent the severity of the same dominant factor: temporal lobe epilepsy, specifically those originating in the left temporal lobe. Years with seizures and seizure frequency can therefore be interpreted in our study as reinforcing factors for the same factor: left temporal lobe epilepsy and represent the severity of this factor.

A complicating factor is the effect of two potential confounding factors: intelligence and educational level. Lateralisation has a clear effect on intelligence with patients with left temporal lobe epilepsy showing lower verbal and total IQ-scores. This is in agreement with many other studies (1, 21, 45, 47). The lower IQ's may be an explanation for the lower memory scores. Vice versa, however, impaired memory, especially verbal memory may lead to a lower verbal IQ and consequently to a lower total IQ (that is largely dependent upon the verbal IQ-score). As this was not a longitudinal developmental study we could not establish the 'direction' of these relationships. There are some arguments that favour the independence of the obtained memory problems from the intelligence scores. Firstly the type of memory problems are specific in expression and show e.g. verbal memory problems in the patients with left temporal lobe epilepsy and impairments on those specific mechanisms that are expected to fail in relation to temporal lobe dysfunctions such as reduced speed of verbal learning and problems consolidating verbal information. Moreover we excluded patients with IQ-scores < 80 to prevent effects of lower intelligence on memory.

The second factor is educational level and we found a lower level of education in those patients with a larger number of years with continuing seizures. Lower educational level may also explain lower memory scores. Nonetheless there are two arguments that contradict an educational-dependent memory deficit. Firstly, one would expect global memory impairment when lack of education would be the dominant factor and not the specific and localization-dependent type of memory impairment found in our study. Moreover, level of education is not different for the left-temporal lobe patients when compared to the other types of epilepsy in this study. Yet the memory impairments are more severe and of a specific type in the patients with left-temporal lobe epilepsy.

We may therefore conclude that epilepsy-related dysfunctions in the temporal lobe are the dominant risk factor for developing memory problems, specifically verbal memory problems (verbal learning and problems consolidating verbal information), with more severe impairments with continuing seizures and when seizure frequency is high.

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CHAPTER 6

Recognition Memory of Serially or Simultaneously Presented Words or Figures Epilepsy Patients with or without Mesial Temporal Sclerosis

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ABSTRACT

Previous studies, examining short term recognition memory in patients with partial seizures as a consequence of mesial temporal sclerosis (MTS) have reported inconsistent findings. Dependent on the paradigms used for measuring recognition memory, some studies have demonstrated that the mesial temporal structures are not critically involved in short term recognition memory. In addition, other studies found a lateralization effect that is consistent with the generally accepted association between left temporal lobe lesions and verbal memory deficits, and right temporal lobe lesions and non verbal memory impairments. In the present study verbal and non verbal recognition memory was tested in 41 patients with left or right temporal lobe epilepsy with MTS (22 left; 19 right) versus 44 patients with left or right temporal lobe epilepsy but without MTS (28 left; 16 right). Verbal and non verbal recognition tasks were presented in both a serial and simultaneous condition to test a hypothesized local/global paradigm.

Multiple analyses of variance (MANOVA) showed that unilateral MTS has no marked effects on verbal or non-verbal recognition memory of patients with seizures. An interaction effect between MTS and the lateralization of epileptic activity was found on memory performance: MTS only leads to deficits in recognition memory in patients with right-sided epileptiform activity. As hypothesized, patients with left temporal lobe abnormalities, have specific deficits with recognizing serially presented information.

INTRODUCTION

The presence of a clearly defined brain lesion as the cause of epileptic seizures is considered to be the crucial risk factor for specific cognitive impairments in patients with epilepsy. The presence of structural damage to the temporal lobe and particularly to mesial temporal structures such as the hippocampus and amygdala is reported to be a key factor for the presence and presentation of memory deficits (Squire & Zola-Morgan, 1991; Baxendale, 1995; Tranel & Damasio, 1995). Especially learning of new episodic information, that is largely dependent on the context in which it is presented, relies on the functional integrity of these mesial temporal systems (Hermann et al, 1992). Mesial temporal sclerosis is the most common cause for refractory temporal epilepsies.

In contrast, the retrieval and recognition of information from semantic memory is considered to be dependent of the integrity of the laterally located cortical structures of the temporal and frontal lobes, and to be independent of the function of the mesial temporal structures (Tranel & Damasio, 1995; Aggleton & Shaw, 1996; Aggleton & Brown, 1999). Nonetheless, not all studies provided confirmation of this distinction and conflicting results have been found. Most studies used the Warrington Recognition Memory Test (WRMT) (Warrington, 1984) for recognition of verbal stimuli (words) and non-verbal stimuli (faces). Miller et al., (1993, 1998) studied the effects of hippocampal sclerosis on the WRMT using recall of words and faces. They did not find impairments on measures of recognition memory. This confirms the independence of recognition memory from mesial temporal structures. In two studies (Hermann, et al., 1995a; Naugel, et al., 1994) the WRMT showed no difference between the recognition results of left versus right temporal lobe patients. This suggests a limited clinical utility of the WRMT as an instrument for the lateralization of dysfunction in this patient group. A similar result was obtained in the study of Baxendale (1997) that also found no significant differences between groups with left or right hippocampal sclerosis, although compared to normal controls the patients of both groups scored below average. A small group of patients had both hippocampal sclerosis and cortical dysgenesis. These patients performed significantly worse on recognition memory than patients with hippocampal sclerosis alone. In contrast, other studies did find a lateralization effect using the WRMT, showing verbal memory deficits with left temporal lobe lesions and non-verbal impairment when damage to the right temporal lobe was found (Morris, et al., 1995). In this

latter study only subjects were used who had undergone a unilateral temporal lobectomy and no pre-surgical data were described. This suggests that the differences may be a result of the surgical intervention itself. Seidenberg et al. (1993) examined pre-post surgical differences and found that left temporal lobe patients are more impaired in recognition memory response discrimination than right temporal lobe patients on the California Verbal Learning Test (CVLT) (Delis, et al., 1987) for verbal episodic learning. The left temporal lobe patients showed specific problems by making more false positives with those items on the list that were semantically related to the target items but were never presented. Helmstaedter & Elger (1996) also used a list learning procedure in patients with temporal lobe epilepsy but found no deficits in recognition memory for words and faces. Recently, Harris et al. (2001) showed that patients with mesial temporal lobe hypometabolism on positron emission tomography (PET) were not impaired on recognition memory for words and designs. However, those patients with a left-sided hypometabolism had impaired delayed recall scores for words after thirty minutes. Patients with right-sided hypometabolism showed no retention problems over delay, but were specifically impaired in learning novel designs.

The relationship between recognition memory and temporal structures, specifically mesio-temporal structures is therefore still under debate. Patients with temporal lobe epilepsies may present an adequate model to study these relationships as some patients have localized damage in the mesio-temporal structures (sclerosis), whereas in patients without mesio-temporal sclerosis seizures originate in larger parts of the temporal lobe. In this study we evaluated results of recognition tests in patients with a unilateral (left vs. right) temporal lobe epilepsy and with or without structural damage of the mesiotemporal structures.

SUBJECTS AND METHOD

Subjects

Patients with a clinical diagnosis of temporal lobe epilepsy, confirmed with EEG, Video-EEG and MRI were included in this study. Patients with structural lesions on the MRI, other than hippocampal sclerosis were excluded from the study.

Many different paradigms have been used for measuring recognition memory. Most studies test verbal versus non verbal recognition memory after multiple trials of free or cued

recall, and short- and long term delayed recall trials. However, the distinction between left and right dysfunction has also to consider the specialization of the left hemispheres for processing serially presented analytic information, whereas the right hemisphere is more involved in processing simultaneously presented holistic information (Levy-Agresti & Sperry, 1968; Bradshaw & Nettleton, 1981; Van Kleeck, 1989). Doyon and Milner (1991) showed that epilepsy patients with a right temporal lobe lesion were less affected when they were instructed to focus their attention on small forms of letters and abstract designs (i.e. local condition), then when they had to concentrate on large forms of this material (i.e. global condition).

4 Recognition tests (as part of the FePsy Neuropsychological Testbattery) were used (Alpherts & Aldenkamp, 1990; Aldenkamp, et al., 1991) were used in this study:

1. Recognition of serially presented words. This task consists of 24 trials in which six well known words are presented serially during a learning phase, with a presentation time of 1 second per item. After a short delay of two seconds the computer generates one of these words between distracters. The patient has to recognize the target item, and indicate in which order this word was presented.
2. Recognition of simultaneously presented words. In this subtest six words are presented simultaneously during a learning phase. After two seconds six words appear, of which one word was shown in the learning phase. The patient has to recognize this target word.
3. Recognition of serially presented figures. This task consists of 24 trials in which four abstract geometric patrons are presented serially during a learning phase, with a presentation time of 1 second per item. After a short delay of two seconds the computer generates a figure between three other distracters. The patient has to recognize the target item, and indicate in which order this target figure was presented.
4. Recognition of simultaneously presented figures. In this subtest four abstract figures words are presented simultaneously during a learning phase. After two seconds a new set of four figures is shown, of which one figure was presented in the learning phase. The patient has to recognize this target figural pattern.

Data analysis

We used the Statistical Packages for the Social Sciences (SPSS) version 9.0 for Windows to analyse the data (Norusis, 1998).

A mixed two 'Pathology' (MTS+ vs. MTS-), by two 'Lateralization' (left vs. right), by two 'Material' (words vs. figures), by two 'Presentation' (serial vs. simultaneous) multivariate analysis of variance (MANOVA), was used to examine the effects of the presence or absence of mesial temporal pathology, and the laterality of the epileptiform activity, on the recognition tests in the different conditions.

We defined MTS+ or MTS-, and the lateralization of the epileptogenic focus as the between subject factors. As within subject factors we used the type of information presented (i.e. words or figures) and the mode of presentation (i.e. serially or simultaneously).

RESULTS

In total 85 patients were consecutively included in this study. Of these patients 50 had a unilateral epileptogenic focus in the left temporal lobe and 35 in the right temporal lobe . MRI-scan indicated a mesial temporal sclerosis (MTS+) in 41 patients (22 left TL; 19 right TL), and in 44 patients (28 left TL; 16 right TL) a mesial temporal sclerosis was absent (MTS-). Demographic and epilepsy characteristics are summarized in Table 6.1.

Statistical testing using χ^2, did not show statistically significant differences for age, gender, and hand preference. Univariate analysis of variance (ANOVA) with MTS and Lateralization as between subject factors, showed a significant correlation between Total IQ and the sum score of the recognition tasks ($F(3,81)=4.202$, $p=0.009$, $\eta=0.135$). Further analysis revealed that only the Verbal and not the Performance IQ has a significant correlation with the recognition tasks.

Table 6.1

Demographic and epilepsy characteristics of the MTS+ and MTS- groups.

	MTS+[a]		MTS-	
	LTL	**RTL**	**LTL**	**RTL**
N	2	19	28	16
Age; years[b]	2,93 (6,4)	40,01 (8,39)	35,47 (10,99)	4,95 (8,64)
Gender;				
male/female	10/12	9/10	16/12	7/9
Hand preference				
right/left/ambidextral	16/8/0	16/3/0	23/3/2	13/2/1
Age at Seizure onset	11,27 (8,28)	19,00 (12,79)	12,94 (10,73)	14,54 (9,92)
Years with seizures	20,27 (7,71)	17,50 (10,47)	19,79 (10,54)	19,38 (11,41)
Seizure Frequency	89,36 (94,06)	103,25 (59,28)	238,11 (565)	97,11 (90,55)
Total IQ	100,57 (12,26)	103,50 (9,12)	104,80 (14,93)	110,33 (12,84)
Verbal IQ	98,71 (11,02)	98,33 (9,00)	101,63 (15,48)	108,46 (13,23)
Performance IQ	103,21 (12,71)	110,00 (12,96)	108,59 (15,78)	110,92 (12,79)

([a]MTS + = mesiotemporal sclerosis as demonstrated with MRI; MTS – no mesiotemporal sclerosis as demonstrated with MRI; LTL = Left temporal lobe epilepsy; RTL = Right temporal lobe epilepsy;

[b] *SD in parentheses)*

A. Effects of within-subjects factors Material (words vs. figures) and Presentation (simultaneously vs. serially).

MANOVA of both within factors (material and presentation) for the total group showed a statistically significant effect for Material (words vs. figures) ($F(1,75) = 90.997$,

p=0.000, η=0.548), as well as Presentation (serial vs. simultaneous) (F (1,75) = 8.058, p=0.006, η=0.097). The analysis shows that the scores on the figural recognition tasks are significantly lower, than the scores on tasks for recognition of words (Table 6.2).

Table 6.2:

Mean scores, standard error, and 95% confidence interval, F and p-value, for the scores on Material: Words vs. Figures for the total group.

			95% confidence interval			
	Mean	**S.E.**	**Lower**	**Upper**	**F**	**p**
Words[a]	16.130	.561	15.013	17.246	90.997	<.001
Figures	12.873	.459	11.959	13.787		

([a] Score: is number correct out of 24 items)

The recognition of figures seems more difficult, than the recognition of words. Furthermore, it seems less difficult to recognize material if this is presented simultaneously compared to serially (Table 6.3).

Furthermore, a statistically significant effect was found for the interaction between Material and Presentation (F (1,75)=111.146, p=0.000, η=0.597). Patients score significantly higher if words are presented simultaneously, compared to serially. However, the recognition of figures is significantly more difficult if these are presented simultaneously (Table 6.4).

Table 6.3:

Mean scores, standard error, and 95% confidence interval, F and p-value, for the scores on Presentation: Serially vs. Simultaneously for the total group.

			95% confidence interval			
	Mean	**S.E.**	**Lower**	**Upper**	**F**	**p**
Serial[a]	13.912	.574	12.769	15.055	8.058	.006
Simultaneous	15.090	.473	14.149	16.032		

([a] Score: is number correct out of 24 items)

Table 6.4:

Mean scores, standard error, and 95% confidence interval, F and p-value, for the scores on Material (Words vs. Figures) and Presentation (Serially vs. Simultaneously) for the total group.

			95% confidence interval			
		Mean	**S.E.**	**Lower**	**Upper**	**F**	**p**
Words[a]	**Serial**	13.966	.661	12.649	15.282	111.146	.000
	Simultaneous	18.294	.566	17.166	19.422		
Figures	**serial**	13.858	.562	12.739	14.977		
	Simultaneous	11.887	.488	10.915	12.859		

([a] Score: is number correct out of 24 items)

B. Effects of between-subject factors Pathology (MTS+ vs. MTS-), and Lateralization (left vs. right).

MANOVA showed no main effects for Pathology: we did not obtain a statistically significant effect of mesial temporal sclerosis ($F(1,75)= 0.490$, $p=0.486$), on the mean total scores of the recognition tasks. Furthermore, we did not find a statistically significant main effect of Lateralization of epileptogenic focus ($F(1,75)= 0.031$, $p=0.860$), on the mean total scores of the recognition tasks.

C. Effects of the interaction between within-subjects factors (Material/Presentation) and between-subjects factors (Lateralization/Pathology).

MANOVA for Pathology (MTS+ vs. MTS-), by Laterality (left vs. right TL), by Material (words vs. figures), by Presentation (serially vs. simultaneously), revealed no significant third or fourth order interactions (i.e. interactions between three or four of these factors), but only second order interactions. As illustrated in table 6.5 we found a second order interaction between mesial temporal sclerosis (MTS+ vs. MTS-) and lateralization of the epileptogenic focus (Left vs. Right) ($F (1, 75) = 4.887$, $p=0.030$, $\eta=0.061$). If there is evidence for MTS, those patients with an epileptic focus in the right temporal lobe score statistically significantly worse on recognition tasks, than patients with a seizure onset in the left temporal lobe. If, however, there is no evidence of mesial temporal sclerosis, patients with EEG abnormalities in the left temporal lobe show statistically significant more impairment than right temporal lobe patients.

Table 6.5:

Mean scores, standard error, and 95% confidence interval, F and p-value, for the interaction between Mesial Temporal Sclerosis (MTS+ vs. MTS-) and Lateralization (Left vs. Right).

				95% confidence interval			
		Mean	**S.E.**	**Lower**	**Upper**	**F**	**p**
MTS-[a]	**Left**	13.010	.840	11.337	14.683	4.887	0.030
	Right	15.361	.963	13.397	17.235		
MTS+	**Left**	15.821	.916	13.996	17.647		
	Right	13.857	1.122	11.622	16.092		

([a] Score: is number correct out of 24 items)

Table 6.6:

Mean scores, standard error, and 95% confidence interval, F and p-value, for the interaction between Lateralization (Left vs. Right) and Presentation (Serially vs. Simultaneously).

				95% confidence interval			
		Mean	**S.E.**	**Lower**	**Upper**	**F**	**p**
Left	**Serial**	13.359	.738	11.888	14.830	5.083	0.027
	Simultaneous	15.473	.608	14.262	16.684		
Right	**Serial**	14.465	.879	12.715	16.216		
	Simultaneous	14.708	.723	13.267	16.149		

([a] Score: is number correct out of 24 items)

Furthermore, a second order interaction was found between Presentation and Lateralization ($F(1,75)=5.083$, $p=0.027$, $\eta=0.063$). Those patients with EEG or MRI abnormalities in the left temporal lobe score significantly lower on the serial recognition tasks (Table 6.6).

Given the fact that Verbal IQ showed a significant correlation with the scores on the recognition tasks, we performed a univariate analysis of variance with VIQ as a covariate (ANCOVA). The analysis has not changed the statistical significant results.

DISCUSSION

All patients have significantly more difficulties with the recognition of serially presented stimuli, compared to simultaneous conditions. This may be related to the fact that in the serial condition patients have to remember not only the stimuli per se, but also the order of presentation in which they appear on the computer screen. This may require more effort for the working memory system. Also, non verbal recognition is more difficult for the patients than the recognition of words (in particular if words are presented simultaneously). Apparently, the recognition of abstract, unknown figures is more difficult to encode and store in short term memory, then recognizing well-known words that are already stored in long term declarative memory. This is, however found for the total group, so independent of the presence of mesial temporal sclerosis and independent of lateralization of the epileptogenic focus.

We have found no main effect of lateralization of epileptiform activity on recognition memory. Patients with a left or right temporal lobe epileptogenic focus do not have statistically significant different scores on recognition memory tasks. Furthermore, there is no interaction between lateralization and type of information (i.e. verbal or non-verbal). Apparently, lateralization of the epileptic focus alone has no effect on recognition memory for verbal or non-verbal information. This is in agreement with the studies of Hermann, et al. (1995a) and Baxendale (1997) who reported that the verbal and nonverbal conditions of the WRMT do not discriminate between left or right temporal lobe patients. The interaction between lateralization of the epileptic focus and presentation mode does have an effect on recognition memory. Patients with a left temporal focus have statistically significant more difficulties in recognizing serially presented (verbal or non verbal) stimuli. This is in

agreement with research from Delis et al. (1986) and Robertson, et al., (1989). The results also confirm the current model in neuropsychology of a specific involvement of the left hemisphere in processing serially presented information. In our study we have not found specific deficits in the recognition of simultaneously presented material for right temporal lobe patients.

The results of our study show that unilateral mesial temporal sclerosis (MTS) as an isolated factor has no marked effects on recognition tasks. This is in agreement with other studies e.g. Aggleton and Shaw (1996), and Aggleton and Brown (1999) who concluded that amnesic patients with focal hippocampal lesions have average scores on recognition tasks. Furthermore, the results are in concordance with the studies of Hermann et al. (1995a) and Baxendale (1997) using the Warrington Recognition Memory Test (WRMT). They concluded that in patients with epilepsy, hippocampal damage (as an isolated factor) does not lead to recognition impairments, which suggests that the medial temporal structures do not play a critical role in recognition memory. Our study did show a statistically significant effect of mesial temporal sclerosis on recognition, only in patients with epilepsy originating in the right temporal lobe. This suggests that that the right mesial temporal lobe structures seem to be more involved in recognition memory than the same structures in the left. This is in agreement with some of the functional imaging studies, including recent studies of our group, showing especially mesial temporal activation in recognition tasks when figural stimuli (that are mostly considered to be dependent upon right temporal function) are used (Martin et al., 1997; Kapur et al., 1995; Deblaere et al., 2002; Aldenkamp et al., 2003).

Our findings have some clinical implications. The most important is that recognition memory may be a more preserved memory function in patients with mesial temporal sclerosis, as compared to the deficits in learning new episodic information. This may be helpful in designing neuropsychological rehabilitation programmes for patients with epilepsy. Secondly, our results suggest that damage to the right temporal lobe may result in deficits in recognition memory. This is important in the presurgical evaluation of patients with right temporal lobe epilepsy.

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CHAPTER 7

Spatial Memory Deficits in Patients after Unilateral Selective Amygdalohippocampectomy

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ABSTRACT

The present study investigated the differential involvement of the right and left hippocampus in various forms of spatial memory: spatial search, positional memory versus object-location binding, and coordinate versus categorical processing. Twenty-five epilepsy patients with selective amydalohippocampectomy were examined using a sensitive computer paradigm to measure these spatial-memory aspects. The patients' performance was compared to a group of thirty healthy controls. The results show that the left amygdalohippocampectomy group performed poorly on the ability to bind together object information to coordinate spatial locations. In turn, the right amygdalohippocampectomy group was impaired in coordinate positional memory. Both patient groups were unimpaired on the spatial search task. These findings are discussed focusing on the "binding device" hypothesis in combination with the cognitive map theory.

INTRODUCTION

It is well established that the medial temporal lobe (MTL) including the hippocampal formation are important in human memory, and are involved in the encoding and storage of information for longer time periods (Squire, 1982). Furthermore, there is ample evidence that the MTL plays a crucial role in the encoding of contextual information in specific. For instance, patients with hippocampal lesions perform poorly on memory task relying on context, such as paired-associate learning and spatial learning (Mayes & Roberts, 2001). The inability to encode and recall contextual information related to the target information is often referred to as source amnesia, and might reflect a problem in binding together multiple aspects of information in memory (Chalfonte et al., 1996). One of the most important contextual features in everyday life is related to spatial characteristics. It is, for example, important to remember where you have left your glasses or your keys, or to search your room effectively in case you have forgotten where they are. Problems in spatial memory can thus result in profound behavioral impairments in everyday life functioning, and are frequently reported in patients suffering from amnesia (Kessels et al., 2000).

Importantly, spatial memory is not a unitary construct, but can be divided into multiple sub-processes, each of which might be selectively impaired in neuropsychological patients. A recent meta-analysis focusing on studies in patients with hippocampal lesions (Kessels et al., 2001) made a distinction between route learning (e.g., remembering a path in a maze), positional encoding (storing coordinates in the form of a cognitive map), object-location memory (recalling the locations of objects in the environments) and spatial working memory (online maintenance of spatial information for a short time period). Furthermore, memory for positional information and memory for bound identity-location information has been found to dissociate in patients with cortical lesions following stroke (Kessels et al., 2002). The results of these previous studies can also be explained by differences in the nature of the spatial relations to be processed (Postma et al., 2004). Specifically, the distinction between categorical and coordinate processing, as proposed by Kosslyn (1994), is relevant here. This theory suggests that the left hemisphere is specialized in the processing of categorical spatial relations (such as above/below or left/right). In turn, the right hemisphere is specialized in coordinate (or "metric") spatial processing (e.g., remembering that the chair is located 2 meters from the window).

To further examine the contribution of the human hippocampus to various forms of spatial memory, a group of medically refractory epilepsy patients was tested who underwent a selective unilateral amygdalohippocampectomy as treatment for the relief of epileptic seizures. Spatial working memory was examined using a computerized spatial search task in which the participant had to search through a number of boxes on the screen in order to find a hidden object. Memory for the locations of objects was studied using a computer task in which positional processing can be separated from object-location binding. Also, the task conditions assess either coordinate processing by means of relocation in free space or categorical processing using pre-marked locations or a grid during relocation (cf. Findlay et al., 1994). The performance of the patients with either left- or right-sided hippocampal lesions was compared to a healthy control group. It could be expected that both amgygdalohippocampectomy groups performs relatively normal on the spatial search task, since spatial working memory function is predominantly subserved by the prefrontal cortex (Fletcher & Henson, 2001), although some studies have found hippocampal involvement in spatial search tasks (Feigenbaum et al., 1996). In contrast, both hippocampal groups were hypothesized to display impairments on the object-location memory task. In line with previous findings in non-hippocampal patients (Kessels et al., 2002a), it might be expected that hemispheric specialization between object-location binding and memory for positional information exists for the hippocampus as well.

SUBJECTS AND METHOD

Subjects

Twenty-five patients receiving periodical out-patient therapy at the Hans Berger Clinic were asked to participate in this study. All patients had suffered from medically refractory temporal-lobe epilepsy caused by mesiotemporal sclerosis (MTS) that was diagnosed with structural magnetic resonance imaging (MRI), and had undergone a unilateral selective amgygdalohippocampectomy for treatment of their seizures. Of these patients, 16 had a left and 9 a right amgygdalohippocampectomy. Presurgically, all patients were investigated according to a phased protocol, which included a thorough medical history, a full neurological examination with a routine EEG and a long-term intericatal and ictal EEG with video monitoring. Furthermore, the patients underwent a intracarotid sodium amytal test (Wada-

procedure) that revealed left-hemisphere language function in all patients. The Dutch version of the Wechsler Memory Scale – Revised (WMS–R; Wechsler, 1987) was performed by all patients as a measure of overall memory performance. The control group consisted of 30 healthy volunteers. Table 1 shows the characteristics of the patient and control group. There were no significant differences between the groups on age ($F(2,52) = 1.4$) or sex distribution ($\chi^2(2) = 5.0$). The control group had a slightly higher education level compared to the patients ($F(2,52) = 4.9$, $p < 0.05$). The left and right surgery groups did not significantly differ with respect to time after operation, age of seizure onset, seizure duration, seizure frequency or performance on the WMS-R index scores (all ts < 1.99). The study was approved by the medical-ethics committee of Utrecht University (University Medical Center) and informed consents were obtained.

Table 7.1:

Characteristics for the left- and right-amgygdalohippocampectomy patients and the healthy controls (age, sex, education level, seizure characteristics, WMS–R performance and time after operation).

	Amygdalohippocampectomy		
	Left (*N*=16)	**Right (*N*=9)**	**Control (*N*=30)**
Age, years[a]	40,2 (9,3)	39,7 (14,9)	45,1 (10,9)
Educational level[b]	4,7 (0,8)	4,9 (0,6)	5,6 (1,0)
Gender (male/female)	10/6	5/4	9/21
Months after surgery	43,9 (33,8)	69,9 (30,1)	
Age at seizure onset	11,3 (8,3)	19,0 (12,8)	
Years with seizures	20,3 (7,7)	17,5 (10,5)	
Seizure frequency[c]	89,4 (94,1)	103,3 (59,3)	
Wechsler Memory Scale-R			
Total Memory Index	87,6 (10,1)	96,7 (12,7)	
Verbal Memory Index	82,8 (13,4)	94,4 (10,7)	
Visual Memory Index	98,8 (13,2)	104,4 (12,6)	

[a] *SD in parentheses;*

[b] *Education level was scored using 7 categories, 1 being lowest (less than primary school) and 7 being the highest (university degree);*

[c] *Seizure frequency reflects the mean total number of seizures per year of active epilepsy)*

Methods

Box Task

The Box Task is a newly developed spatial search task based on the principle of spatial search tasks such as the Executive Golf Task (Feigenbaum et al., 1996). Pictures of closed boxes (size approximately 1 × 1 cm) were displayed at different locations within a 19 × 19 frame on a 15″ touch-sensitive LCD computer monitor. A target object (e.g., shoe, umbrella) was visible at the bottom of the screen. The participant was instructed to search through the boxes until the target object (which is also hidden inside one of the boxes) was found. Clicking a box (using the touch-sensitive screen) resulted in the "opening" of that box, displaying either an empty box or the object that had to be found. An empty box closed again in 2 seconds. If the target object was found, a new target object was displayed on the bottom of the screen and the box containing the previous target was closed again. All previously found target objects within a trial remained hidden inside their box; the participant had to remember which boxes had already been searched, as well as which boxes already contained target objects. Thus, all the boxes on the screen were subsequently "filled" with target objects. Hereafter, the next trial started using a new spatial layout (one trial consisted of multiple searches in the same spatial layout). The number of boxes increased after two different trials with the same number of boxes (resulting in set sizes of 4, 6 or 8 boxes). The task begun with two practice trials containing only three boxes. Two types of errors were possible (see also Feigenbaum et al., 1996). First, a *within-search error* occurred if the subject returned within one search to a previously opened box which did not contain the target object. This measure reflects the ability to actively keep spatial information "online" during a search. Second, a *between-search error* occurred if the subject returned to a box which contains a target item from a previous search. This measure assesses the ability to maintain spatial information over longer time periods within working memory (possibly linked to storage into long-term memory).

Object Relocation

To assess memory for the locations of objects, the Object Relocation program was used (Kessels et al., 1999) to present stimulus displays containing ten everyday objects (size approximately 1 × 1 cm) at different spatial locations within a 19 × 19 cm frame (also on the 15″ touch-sensitive LCD computer screen). Each stimulus display was presented for 30 seconds, after which the frame was emptied and the objects were made visible on top of the

frame. The participant was instructed to relocate the objects to their previously occupied locations within the frame, with no time restrictions, using the touch-sensitive screen. Four spatial memory conditions were included, measuring either object-location binding or positional memory, and categorical or coordinate processing. In the categorical object-location binding (*Categorical-OLB*) condition, 10 different objects were shown at different locations. Subsequently, the locations of the objects were marked with black dots, and the subject had to assign the objects to their previously occupied locations. Here, the percentage incorrectly relocated objects in a stimulus display was used as error score. In the categorical positional (*Categorical-POS*) condition, ten identical objects were presented at different locations. In the subsequent relocation phase, a 7 × 7 grid was present, and the objects had to be relocated to their previously occupied locations (note that the grid was visible in the relocation phase only). The percentage incorrectly placed objects was calculated (i.e., within the correct cell or not). In the coordinate object-location-binding (*Coordinate-OLB*) condition, again ten different objects were presented at different locations, which had to be relocated subsequently in an empty frame (with no grid or pre-marked dots present). Here, the absolute deviation in mm was computed for a stimulus display as a whole (the total differences between the objects' original and relocated positions). Finally, the presentation phase of the coordinate positional (*Coordinate-POS*) condition was the same as the Categorical-POS condition, but no grid was present in the relocation phase. Thus, the exact locations had to be relocated as accurately as possible in an empty frame. Since only positions were presented without object information, it is difficult to determine which relocated position belongs to which original position in order to calculate the absolute deviation in mm. Theoretically, it would be possible to assign each relocated object to the original position that is nearest, but the results of this calculation cannot be easily interpreted. Therefore, the best fit score was computed: all possible configurations between original and relocated positions are computed, and the fit that has the smallest error rate is considered to be the best fit configuration (Kessels et al., 1999). This best-fit score reflects positional reconstruction, taking into account possible rotations and shifts. Each task condition consisted of two trials using different spatial layouts and different objects, and was preceded by a practice trial using only four objects and locations. The order of the task was fixed to minimize possible order effects (Kessels et al., 2002).

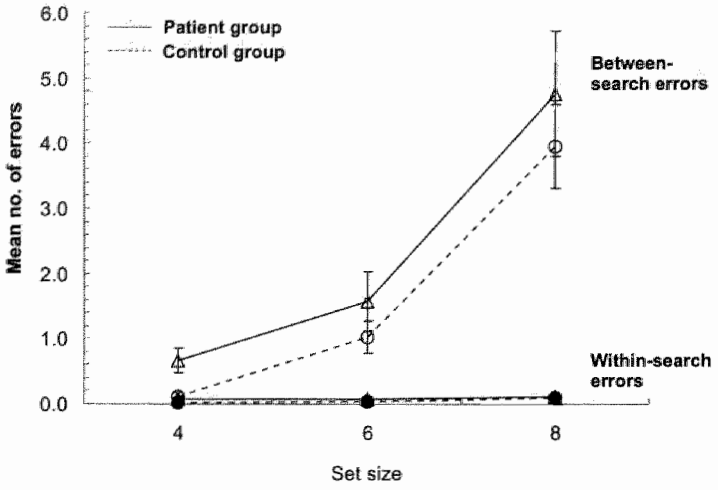

Figure 7.1:

Mean (+ SEM) number of within-search and between-search errors for the amydalohippocampectomy and the control group on the Box Task for the three set sizes (4, 6 and 8 boxes).

RESULTS

Figure 1 shows the results for the Box Task. Within-search errors were analyzed using a repeated-measures General Linear Model (GLM) with Set Size (4, 6 or 8 boxes) as within-subjects factor and Group (left-sided surgery, right-sided surgery and control) as between-subject factor. Overall, a main effect of Set Size was present ($F(2,47) = 9.0, p < 0.0005$), indicating a significant (but small) increase in within-search errors if more boxed had to be searched. No Group effect or Group × Set Size interactions were present (Fs < 1.23). For the between-search errors, a GLM was performed using the same factors. Again, a Set Size effect was found ($F(2,47) = 22.9, p < 0.0005$) showing an increase in errors if more boxes had to be searched. No overall Group effect or Group × Set Size interaction was found (Fs < 1.5).

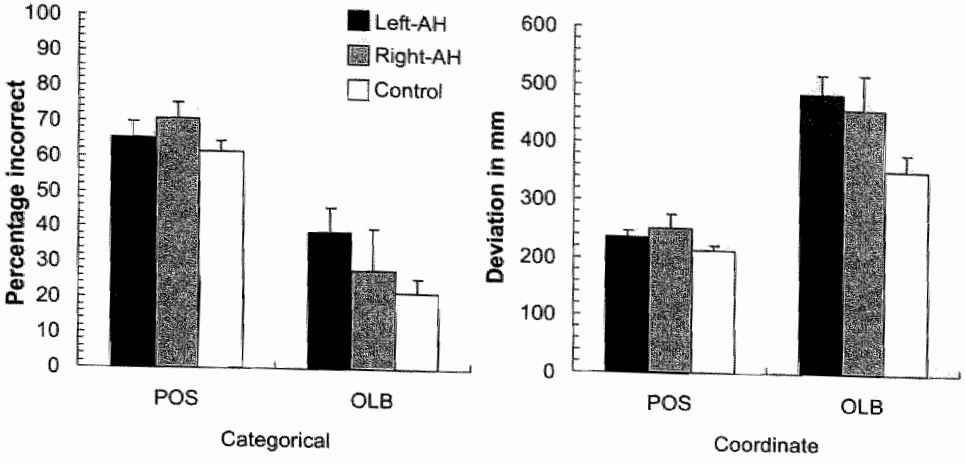

Figure 7.2:

Mean (+ SEM) percentage incorrectly placed objects for the categorical positional (POS) and the categorical object-location binding (OLB) condition, and mean (+ SEM) deviation in mm for the coordinate POS and the coordinate OLB conditions for the left and right amgygdalohippocampectomy (AH) patients and the control group.

Figure 2 shows the results for the Object Relocation conditions. A GLM revealed Group effects on the Coordinate-POS condition ($F(2,49) = 3.5$, $p < 0.04$) and the Coordinate-OLB condition ($F(2,49) = 4.3$, $p < 0.02$), but not on the Categorical-POS ($F(2,49) = 1.0$) and Categorical-OLB ($F(2,49) = 2.1$) conditions. Post-hoc Dunnett t tests with the control group as reference showed that the left-sided amgygdalohippocampectomy group performed worse than the control group on the Coordinate-OLB condition ($p < 0.008$), whereas the right-sided amgygdalohippocampectomy group performed worse than the controls on the Coordinate-POS condition ($p < 0.031$) selectively.

DISCUSSION

The purpose of the present study was to investigate the contribution of the right and left hippocampus to various forms of memory for the location of objects. Clearly, the findings demonstrate selective and lateralized impairments in various spatial-memory components. First, no impairments were found on the spatial search task; neither in the ability to actively manipulate information online (as measured by the within-search score) nor in the ability to maintain information over longer time periods (the between-search performance). Although some studies have identified hippocampal involvement in spatial search tasks (e.g., Feigenbaum et al., 1996), the current finding is in agreement with the notion that other cortical areas than the hippocampal formation are specialized in spatial search processes, for example the prefrontal cortex (Fletcher & Henson, 2001).

Second, the left amgygdalohippocampectomy group showed an impaired performance on the condition which assesses the ability to bind together coordinate location information and object-identity information within memory. This supports the hypothesis of the left hippocampus being a "binding device", which has been proposed by several authors, based on either animal experiments (Eichenbaum & Bunsey, 1995) or on studies in amnesic patients (Chalfonte et al., 1996). With respect to possible lateralization effects of hippocampal involvement in binding, a recent fMRI study demonstrated that specifically the left anterior hippocampal area was activated during a task condition requiring the binding of objects to locations, but not during trials in which only object information or only spatial information had to be remembered (Mitchell et al., 2000). This is in line with the current finding that left amgygdalohippocampectomy patients show a selective problem in binding objects to coordinate locations.

Third, the right amgygdalohippocampectomy group performed worse than the controls on the condition which involves coordinate positional processing. This is in agreement with O'Keefe and Nadel's (1978) influential theory originating from studies in rats, suggesting that the right hippocampus stores this type of spatial information in the form of an allocentric cognitive map. This hypothesis was recently studied in patients with hippocampal lesions (Holdstock et al., 1999), providing further evidence for a hippocampal contribution to allocentric spatial memory. The present results do not show hippocampal involvement in the processing of categorical spatial relations. It might be argued that tasks assessing categorical

processing (i.e., a mental representation that consists of categories rather than a continuous positional map) are merely less sensitive than coordinate tasks. However, selective effects on categorical spatial memory conditions have been found in previous studies (Alexander et al., 2002; Kessels et al., 2002b). Thus, the current findings suggest that categorical spatial-memory processing is primarily subserved by non-hippocampal brain areas (cf. Kosslyn, 1994).

Only a few studies have used spatial-memory tasks that rely only on metric processing, that is, without any semantic content. More studies have examined spatial memory for a combination of positional information and object identities. For example, various authors have investigated the relocation of toy objects on a table top in patients with hippocampal lesions, commonly demonstrating a right-hippocampal involvement (Smith & Milner, 1989; Nunn et al., 1999). In general, the current findings corroborate and extend previous results with similar paradigms. For example, a study in patients with unilateral cortical stroke demonstrated left-hemisphere involvement in object-location binding and right-hemisphere involvement in coordinate spatial processing (Kessels et al., 2002a). Moreover, preliminary results in amgygdalohippocampectomy patients (Köylü et al., 2003) indicate that left-sided surgery patients were impaired on both object-location binding and positional memory, whereas right-sided surgery patients was impaired on positional only. Although the latter results also show a differential hemisphere-dependent involvement in various aspects of spatial memory, our present findings do not show entirely the same pattern as in the study of Köylü and colleagues (2003). This discrepancy might be due to the fact that the Köylü study probably focused on more sub-acute postoperative effects. It is possible that a relatively short period after the operation results in more severe memory problems caused by more diffuse effects of the surgical treatment itself, and that selective effects are more likely to be found in the chronic post-operative state.

Also, the present results support the notion that remembering the locations of objects can be both functionally and neuroanatomically dissociated from merely remembering positions. Originally, it was hypothesized that remembering the locations of objects requires an integration process of both positional memory and the binding of object information to given locations. Hence, an impaired performance on positional memory would automatically result in impaired coordinate object-location binding. However, no empirical evidence for such an integration process has been found either in group studies (Kessels et al., 2002a) or in

individual cases (Kessels et al., 2002b). Finally, it should be noted that the lesions in the current patient group were not limited to the hippocampus, but also included the amygdala. However, as a result of the proximity of the hippocampus and the amygdala in the brain, it is difficult to separately examine possible differential effects of lesions in these specific areas using neurosurgical patients or neuroimaging techniques.

In sum, the present results show that, in line with the cognitive map theory, the right hippocampus is involved in coordinate spatial-memory processing, and that the left hippocampus acts as a binding device. No evidence was found of hippocampal involvement in categorical spatial-memory processes. The current findings also emphasizes the importance of detailed clinical assessment of spatial-memory function in MTL epilepsy patients as part of a pre- and post-operative neuropsychological assessment, which is currently rarely performed. Moreover, the application of these experimental tasks in combination with other ecologically valid spatial-memory tests may lead to a better understanding of the subjective memory problems many of these patients experience in daily life.

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CHAPTER 8

Summary

SUMMARY

The main scope of this thesis has been to study different aspects of memory functions in a relatively large population of epilepsy patients with subjective memory complaints who are treated in the epilepsy centres in the Netherlands.

The following key objectives were set at the start of this prospective multi-centre study:

- An analysis of the memory complaints patients experience and the relationship between memory complaints and epilepsy-related factors.
- Describing different memory profiles using accepted memory subsystems.
- Exploring the effects of epilepsy-related factors on these memory subsystems and finding the dominant risk factors for developing memory impairments.
- Examining short term recognition memory in patients with epileptic seizures as a consequence of mesial temporal sclerosis (MTS).
- Investigating the differential involvement of the right and left hippocampus in various forms of short term spatial memory in patients who underwent a unilateral selective amygdalohippocampectomy.

In *Chapter 3* the results of the analysis of the memory complaints are described. Memory complaints were measured with the GKLE (*de Geheugenklachtenlijst voor Epilepsie),* which is a standardized memory questionnaire for patients with epilepsy. Using subjective memory complaints as an inclusion criterion our study group consisted mainly of patients with a chronic refractory localisation related epilepsy with a temporal origin. As expected, patients experienced significantly more memory complaints. They particularly complained about memory problems that reflect ' absentminded behaviour ', such as forgetting where a certain object has been put, or often checking one's pocket to find something. Furthermore, they indicated the retrieval of complex meaningful information (i.e. being able to remember an experience or story, or forget people's names) as a specific memory problem. Patients

complained less about childhood memory, like for instance 'remembering a child they used to play with as a child'.

Remarkably, the pattern of memory complaints showed no relationship with most epilepsy-related factors, (i.e. age at onset, etiology, localisation of seizures, type of seizures, antiepileptic medication). Only, those patients with a long duration of active epilepsy complained significantly more about retrieving information from memory.

In contrast, we did find a strong tendency to present memory complaints for older patients, with higher intellectual functions, who subjectively experience more emotional problems in the area of neuroticism. Memory complaints may thus be seen as a general 'psychosomatic' reaction to a clinic epilepsy and only in patients who experience consequences of memory loss in daily life.

Within this group of patients who are at increased risk of such memory complaints we studied the different memory profiles, using the accepted memory subsystems, i.e. Verbal Short Term Memory (VSTM), Verbal Long Term Memory (VLTM), Non verbal Short Term Memory (NvSTM), and Non verbal Long Term Memory (NvLTM). The results described in *Chapter 4* showed that patients with left temporal lobe epilepsy are clearly more at risk for memory impairments, compared to patients with right temporal lobe epilepsy. Furthermore, both groups show different memory profiles and risk patterns for memory deficits.

Based on the memory profile it can be concluded that left temporal lobe epilepsy has a negative functional impact on all four memory subsystems, although impairments in the domain of verbal memory are the most prominent. These patients have specific deficits in the association and acquisition of verbal episodic information that is presented auditory and may be interpreted primarily as a deficit in the storage process. Patients with left temporal lobe epilepsy also show specific deficits in clustering verbal information on their semantic correspondence. Although, this may also suggest a basic deficit in language functions underlying verbal memory impairments, in our study vocabulary is within the normal range of the population in both groups.

We did not find systematic impairments in NvSTM or NvLTM, in both groups. Although, this is in line with results in many clinical studies, we have argued that the inconsistent relationship between right temporal lobe epilepsy and non verbal memory

deficits may be partly explained by the insufficient sensitivity of the tests used. This is also illustrated in *Chapter 7*.

In addition to exploring in which of the memory subsystems the epilepsy patients show impairments, we studied the effects of the epilepsy-related factors such as, type of epilepsy, site and side of focus localization, age at onset, years of continuing seizures, seizure type, seizure frequency, and antiepileptic medication, on their performances on a broad neuropsychological test battery for memory functions. *Chapter 5* describes he results of this study.

In the total sample of 252 patients with epilepsy no statistical effects of the epilepsy-related factors on memory were found. This finding may be confounded by the heterogeneity of the total patient sample and the relatively small subgroups of patients with extratemporal foci or bilateral foci, as a consequence of the clinical inclusion method.

By focusing exclusively on patients with unilateral temporal focus localization, we found that lateralisation is the crucial risk factor; i.e. patients with a left temporal lobe epileptic focus have significantly increased risk of especially impairment of verbal and delayed memory. The main effect of lateralisation appeared to be independent of the other epilepsy-related factors influencing memory i.e. 'seizure frequency' and 'years with seizures'. A high seizure frequency specifically impairs the first encoding stage of the memory process. Finally, we found that the factor 'continuing seizures', i.e. having more than 30 years with seizures, is related to verbal and non verbal memory impairment, and delayed recall. The effect was also independent from the other factors.

Although, the effects of 'seizure frequency' and 'years with seizures' are independent, 'lateralisation' has a much stronger effect. While patients were not selected on the basis of the epilepsy-related factors, but because they subjectively complained about memory problems, these factors may concern temporal lobe seizures and therefore represent a more general dominant factor: temporal lobe epilepsy specifically lateralised to the left.

In addition to these clear relationships with epilepsy-related factors, we found that intelligence and educational level are two potential confounding factors. Lateralisation has a clear effect on intelligence of patients with left temporal lobe epilepsy showing lower verbal and consequently total IQ-scores. Furthermore, we found a lower educational level in those patients with a larger number of years with continuing seizures. However, in chapter 5 it is

argued that the obtained memory impairments may be independent from both confounding factors.

So far these studies reconfirm that patients with temporal lobe epilepsy and higher risk for developing specific deficits in the association and acquisition of verbal episodic information, as a deficit in the storage process. The results in previous studies examining short term recognition memory in patients with mesial temporal lobe epilepsy are inconsistent. Short term recognition memory was studied with a computer paradigm in patients with left or right temporal lobe epilepsy with or without Mesial Temporal Sclerosis (MTS). Verbal and non verbal recognition tasks from the FePsy battery were presented in both a serial and simultaneous condition to test a hypothesized local/global paradigm. MTS as an isolated factor has no marked effects on recognition tasks, which suggest that the medial temporal structures do not play a critical role in recognition memory. However, there was in interaction effect between MTS and lateralization of the epileptic focus. A statistically significant effect of MTS on recognition memory was found only in patients with seizures originating in the right temporal lobe. Lateralization of the epileptogenic focus has no statistically significant main effect on the performances of recognition memory tests of the patients. Furthermore, we found no interaction between lateralization and the type of information presented.

Recognition memory may be more preserved in patients with MTS, as compared to the impairments in the acquisition of information.

In *Chapter 7* the results are described of a study on the differential involvement of the right and left mesial temporal lobe on various forms of spatial memory: spatial search, positional memory versus object-location binding, and coordinate versus categorical processing. The test performances on computerised tests measuring these aspects of spatial memory of twenty-five patients, who underwent a selective amydalohippocampectomy for treatment of their seizures, were compared to healthy controls. The findings demonstrate selective and lateralized impairments in various spatial-memory components. A left amydalohippocampectomy resulted in an impaired ability to bind together object information to coordinate spatial locations. Those patients who underwent a right

amydalohippocampectomy performed worse on the condition which involves coordinate positional processing. Both patient groups were unimpaired on the spatial search task.

HOOFDSTUK 8

Samenvatting

SAMENVATTING

In deze dissertatie worden de onderzoeksresultaten beschreven van een studie naar verschillende aspecten van het functioneren van het geheugen, in een relatief grote populatie van 252 patiënten met epilepsie die subjectief geheugenklachten ervaren in het dagelijks leven. Alle patiënten worden behandeld in één van de epilepsiecentra in Nederland.

De volgende specifieke onderzoeksvragen werden voorafgaand aan dit prospectief onderzoek geformuleerd:

- Welke geheugenklachten worden door deze epilepsiepatiënten ervaren en wat is de relatie tussen geheugenklachten en aan de epilepsie gerelateerde factoren?
- Is er sprake van onderscheidbare geheugenprofielen, uitgaande van de binnen de neuropsychologie geaccepteerde geheugensysteem?
- Is er een relatie tussen specifieke geheugenstoornissen en de aan epilepsie gerelateerde factoren, en kunnen risicofactoren worden beschreven voor het ontwikkelen van geheugenstoornissen bij deze epilepsiepatiënten?
- Zijn er aanwijzingen voor een beperking van de recognitie op korte termijn bij epilepsiepatiënten met aanvallen als gevolg van een mesio-temporale sclerose (MTS)?
- Is er sprake van een gedifferentieerde functionele betrokkenheid van de linker en rechter hippocampus bij diverse vormen van spatiële kortetermijngeheugen taken, bij patiënten die een unilaterale selectieve amydalohippocampectomie ondergingen als behandeling voor de epilepsie?

In *Hoofdstuk 3* worden de resultaten beschreven van de analyse naar de geheugenklachten. De geheugenklachten van de epilepsiepatiënten zijn gemeten met de GKLE (*de Geheugenklachtenlijst voor Epilepsie).* Dit is een gestandaardiseerde vragenlijst naar geheugenklachten, specifiek ontwikkeld voor epilepsiepatiënten.

Doordat in dit onderzoek het subjectief ervaren van geheugenproblemen als inclusiecriterium is gehanteerd, bestond de onderzoekspopulatie voor een groot deel uit patiënten met een chronische, refractaire epilepsie, waarbij de aanvallen gelokaliseerd zijn in de temporaal kwab. Zoals verwacht, signaleerden de patiënten in vergelijking met een theoretische controlepopulatie significant meer geheugenklachten. Patiënten ervaren vooral geheugenproblemen die 'absentminded behaviour' reflecteren. Hierbij kan gedacht worden aan het vergeten waar een bepaald voorwerp is neergelegd, of het onnodig meerdere keren controleren van je broek- of jaszak om een voorwerp terug te vinden. Ook geven zij aan het opdiepen van complex betekenisvolle informatie, zoals het zich herinneren van een ervaring of verhaal, of het onthouden van namen en gezichten, als een specifiek cluster van klachten te ervaren. Epilepsiepatiënten signaleren de minste problemen met het onthouden van informatie die gerelateerd is aan de kindertijd, zoals het onthouden van een vriendje of vriendinnetje waarmee men als kind gespeeld heeft.

Opmerkelijk is dat het patroon van geheugenklachten geen enkele samenhang vertoont met de aan epilepsie gerelateerde factoren, zoals debuutleeftijd, etiologie, lokalisatie van de aanvallen, type aanvallen, en de voorgeschreven anti-epileptica. Uitsluitend patiënten met een lange duur van actieve epilepsie geven significant meer klachten aan over het terughalen van informatie.

In dit onderzoek is een duidelijke tendens geconstateerd dat oudere patiënten (dat wil zeggen tot een maximale leeftijd van 60 jaar), met hogere intellectuele capaciteiten, die subjectief meer aan neuroticisme gerelateerde emotionele problemen ervaren, geheugenklachten signaleren.

Binnen deze groep patiënten met een verhoogd risico op geheugenproblemen zijn verschillende geheugenprofielen onderzocht. Hierbij is uitgegaan van de binnen de klinische neuropsychologie geaccepteerde geheugensubsystemen: Verbaal Kortetermijngeheugen (VSTM), Verbaal Langetermijngeheugen (VLTM), Non verbaal Kortetermijngeheugen (NvSTM), en Non verbaal Langetermijngeheugen (NvLTM).

De resultaten zoals beschreven in *Hoofdstuk 4* geven sterke aanwijzingen voor het feit dat vooral de patiënten met een links temporaal gelokaliseerde epilepsie een verhoogd risico op geheugenstoornissen vertonen, in vergelijking met patiënten met een rechts temporaal

gelokaliseerde epilepsie. Beide groepen hebben een verschillend functioneel geheugenprofiel en risicopatroon voor geheugenstoornissen.

Gebaseerd op het gevonden geheugenprofiel wordt de conclusie getrokken dat een links temporale epilepsie een negatieve functionele invloed heeft op alle vier de geheugensystemen, ofschoon stoornissen in het domein van het verbale geheugen het meest prominent zijn. Deze patiënten hebben specifieke beperkingen in de associatie en acquisitie van verbaal episodische kennis die auditief wordt gepresenteerd, hetgeen primair als een stoornis van het opslagproces kan worden beschouwd. Patiënten met een links temporale epilepsie vertonen specifieke beperkingen in het clusteren van verbale informatie, op basis van de semantische overeenstemming. Ofschoon dit zou kunnen suggereren dat een specifieke beperking van de taalfuncties ten grondslag ligt aan de verbale geheugenstoornissen, zien we in deze studie dat de actieve woordenkennis van de onderzochte populaties niet afwijkt van de normprestaties van de theoretische controlepopulatie.

In deze studie werden geen systematische beperkingen geconstateerd van het NvSTM of het NvLTM, in beide groepen. Hoewel dit in overeenstemming is met de resultaten van vele klinische studies, wordt de veronderstelling naar voren gebracht dat de inconsistente samenhang tussen een rechts temporale epilepsie en een non verbale geheugenstoornis deels verklaard kan worden door een geringe sensitiviteit van de gebruikte tests. Ook in *Hoofdstuk 7* wordt deze veronderstelling geïllustreerd.

Naast een exploratie van de verschillende geheugensystemen welke specifieke beperkingen laten zien bij epilepsiepatiënten, is onderzocht wat de effecten zijn van de aan epilepsie gerelateerde factoren als, type epilepsie, lokalisatie van het epileptisch focus, debuutleeftijd, aantal jaren met actieve epilepsie, aanvalstype, aanvalsfrequentie, en de behandeling met anti-epileptica, op de testprestaties van onderzoekspopulatie. In *Hoofdstuk 5* worden de resultaten van deze studie beschreven.

In de totale onderzoekspopulatie van 252 patiënten met epilepsie worden geen statistisch significante effecten van de epilepsie gerelateerde factoren op de objectieve geheugenscores gevonden. Dit staat mogelijk in verband met de heterogene samenstelling van de totale onderzoekspopulatie en de relatief kleine subpopulaties van patiënten met een extratemporaal of bilateraal epileptisch focus, als consequentie van de gehanteerde klinische inclusiecriteria.

Na exclusie van deze laatste twee subpopulaties zijn de prestaties van uitsluitend de patiënten met een unilateraal temporaal focus geanalyseerd. Hierbij is gebleken dat de lateralisatie van het epileptisch focus de meest cruciale risicofactor betreft; patiënten met een links temporaal epileptisch focus vertonen een significant groter risico op (met name verbale) geheugenstoornissen.

Dit hoofdeffect van lateralisatie is onafhankelijk gebleken van de andere aan epilepsie gerelateerde factoren 'aanvalsfrequentie' en 'aantal jaren met actieve epilepsie', die bij dit onderzoek eveneens een statistisch significant resultaat laten zien. Een hoge aanvalsfrequentie hangt specifiek samen met een stoornis in de encoderingsfase van het geheugenproces. Ten slotte worden aanwijzingen gevonden voor het feit dat bij epilepsiepatiënten met een meer dan 30 jaar actieve epilepsie, het leren van verbale en non verbale informatie en de uitgestelde herinnering hiervan, significant meer beperkt is dan bij patiënten die een geringer aantal jaren met aanvallen hebben doorgemaakt.

Ofschoon ook deze beide effecten onafhankelijk waren, is het effect van 'lateralisatie' duidelijk sterker. Omdat patiënten niet zijn geselecteerd op basis van de aan epilepsie gerelateerde factoren, maar omdat zij subjectief klachten ervaren over het functioneren van hun geheugen, is het mogelijk dat deze factoren een meer algemene dominante factor representeren, namelijk een links temporaal gelokaliseerd temporale epilepsie.

Naast deze duidelijke samenhang met klinische epilepsiefactoren, is gebleken dat (verbale) intelligentie en opleidingsniveau twee potentiële storende factoren zouden kunnen zijn. Lateralisatie heeft een statistisch significant effect op intelligentie bij patiënten met een links temporale epilepsie. Deze groep heeft een lager verbaal IQ, op basis waarvan ook het totaal IQ lager is dan dat van de rechts temporale epilepsiepatiënten. Tevens, hebben de patiënten met een groter aantal jaren met actieve epilepsie een geringer opleidingsniveau. Overigens wordt in hoofdstuk 5 beargumenteerd dat de geconstateerde geheugenstoornissen onafhankelijk zijn van beide storende factoren.

Tot zo ver bevestigen de resultaten van deze studies dat patiënten met een temporale epilepsie een substantieel groter risico hebben op het ontwikkelen van specifieke beperkingen in de acquisitie en associatie van verbaal episodische informatie, als een indicatie voor een stoornis in het opslagproces van geheugen.

De conclusies uit eerder onderzoek naar de recognitie op korte termijn van patiënten met een mesio-temporale epilepsie zijn echter minder consistent. Recognitie op korte termijn is onderzocht met een computer paradigma bij patiënten met een links of rechts temporale epilepsie, met of zonder een mesio-temporale sclerose (MTS) en worden beschreven in *Hoofdstuk 6*. Deze patiënten kregen verbale of non verbale recognitietaken uit de FePsy-testbatterij aangeboden. Beide taken werden in een seriële en simultane conditie gepresenteerd, om te kunnen toetsen of eventuele beperkingen gerelateerd zijn aan tekorten in het zogenaamde 'local/global paradigma'.

MTS als een geïsoleerde factor blijkt geen effect te hebben op de prestaties op de recognitietaken, wat suggereert dat de mediale temporale hersenstructuren geen kritieke rol spelen in de recognitie op korte termijn. Echter, er wordt wel een interactie-effect tussen MTS en lateralisatie van het epileptisch focus geconstateerd. Een statistisch significant effect van MTS op recognitietaken wordt gevonden, alleen bij die patiënten bij wie de aanvallen in de rechter temporaalkwab ontstaan.

Lateralisatie van het focus heeft geen statistisch significant hoofdeffect op de prestaties op recognitietaken. Tevens wordt er geen interactie-effect tussen lateralisatie en het type informatie geconstateerd.

Geconcludeerd wordt dat de recognitie op korte termijn minder beperkt is, in vergelijking met de stoornissen in de acquisitie van informatie.

In *Hoofdstuk 7* worden de resultaten weergegeven van een onderzoek naar de functionele betrokkenheid van de linker en rechter temporaalkwab bij verschillende vormen van spatieel geheugen, te weten: spatieel zoeken, positioneel geheugen versus objectlocatiegeheugen, en metrische versus categoriale informatieverwerking. Deze aspecten zijn met een gecomputeriseerd testparadigma onderzocht bij 25 patiënten die een selectieve amydalohippocampectomie ondergingen als behandeling van hun partiële aanvallen, en vergeleken met een groep gezonde controles.

De bevindingen laten inderdaad zien dat er selectieve en gelateraliseerde beperkingen in verschillende componenten van het spatiële geheugen optreden.

Een amygdalohippocampectomie in de linkerhemisfeer lijkt het vermogen te verstoren om een associatie te maken tussen specifieke objectinformatie en de coördinaten van de spatiële locatie waar het object zich bevindt. Echter, patiënten die een rechtszijdige amydalohippocampectomie ondergingen presteerden significant slechter op de conditie waarbij de metrische aspecten van het objectlocatiegeheugen werden gemeten. Beide groepen presteerden in vergelijking met de controles niet slechter op de spatiële zoektaak.

PUBLICATIONS

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Marc Hendriks, 21 november 2004

CURRICULUM VITAE

Marc Hendriks is geboren op 20 augustus 1964 te Tilburg. Hij groeit op in Goirle, waar hij het Hoger Algemeen Voortgezet Onderwijs volgt aan het "Mill-Hill College". Na in 1982 hiervan het diploma te behalen, schrijft hij zich in bij de Sociale Academie "Markendaal" in Breda voor de opleiding maatschappelijk werk. Dit bleek al snel niet de juiste keuze, zodat hij de overstap maakt naar de studie psychologie aan de Katholieke Universiteit Brabant in Tilburg. Hij volgt het doctoraalprogramma van de specialisatie Neuropsychologie bij Prof. Dr. Van der Vlugt en in dit kader krijgt hij in oktober 1986 een klinische stageplaats aangeboden in het epilepsiecentrum "Dr. Hans Berger Kliniek", te Breda. Als één van de initiatiefnemers van het zogenaamde COS-programma voor kinderen met leer- en gedragsproblemen als gevolg van cerebraal disfunctioneren, treedt hij in augustus 1987 in dienst van Hans Berger Kliniek om het COS-programma verder te ontwikkelen. Na dit intermezzo behaalt hij in juni 1988 het doctoraaldiploma psychologie en krijgt een baan als neuropsycholoog in de Hans Berger Kliniek aangeboden, waar hij tot december 2002 werkzaam zal blijven. Vanaf die tijd is hij in dezelfde functie werkzaam in het epilepsiecentrum Kempenhaeghe, te Heeze.

In april 1997 wordt hij als GZ-psycholoog in het BIG-register ingeschreven en in diezelfde maand accepteert hij een aanstelling als universitair docent Neuro- en Revalidatiepsychologie aan de Radboud Universiteit in Nijmegen.

Naast deze functies heeft hij zitting in de opleidingscommissie voor de specialistische postacademische opleiding tot Klinisch Psycholoog. Verder is hij lid van de commissie "Neuropsychologische Diagnostiek Testgebruik" van de sectie Neuropsychologie van het Nederlands Instituut voor Psychologen (NIP), de commissie "Onderzoek en Ontwikkeling" van de sectie Revalidatiepsychologie van het NIP, en de Commissie Testaangelegenheden Nederland (COTAN) van het NIP. Tenslotte is hij redactielid van het tijdschrift "Epilepsie".